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Neonatal Seizures: Practical Approaches to Classification, Diagnosis, and Management

Amanda G. Sandoval Karamian[1], Ronit Pressler[2], Cecil D. Hahnr[3], Hans Hartmann [4], Jo Wilmshurst[5] and Courtney J. Wusthoff[6]

[1]Children's Hospital of Philadelphia, Division of Neurology, 3501 Civic Center Blvd Office 1200.12, Philadelphia, PA 19104
[2] Great Ormond Street Hospital for Children, Great Ormond Street, London WC1N 3JH
[3] Division of Neurology, The Hospital for Sick Children, Department of Paediatrics, University of Toronto, Toronto, Canada [4] Clinic for Pediatric Kidney, Liver and Metabolic Disorders, Hannover Medical School, Hannover, Germany
[5] Department of Paediatric Neurology, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town, South Africa
[6] Stanford Child Neurology, 750 Welch Road, Suite 317, Palo Alto, CA 94304 USA

Corresponding author: Amanda G. Sandoval Karamian; sandovalka@email.chop.edu

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Abstract

Neonatal seizures are the most common manifestation of neurological illness in newborns, yet their accurate diagnosis and management remain challenging. This is particularly true in resource-limited settings. In this symposium, members of two International League Against Epilepsy (ILAE) task forces on classification, diagnosis, and treatment of neonatal seizures presented a novel, evidence-based framework for the diagnosis and classification of neonatal seizures that integrates clinical signs and electroencephalographic findings to specify varying levels of diagnostic certainty. The wide spectrum of neonatal seizures is illustrated, as well as common management challenges, and practical evidence-based management strategies that can be tailored to a wide range of practice settings.

Keywords: infant, newborn, neonate, seizure, hypoxic-ischemic encephalopathy, electroencephalography, anticonvulsants.

Definition and Classification of Neonatal Seizures: Insights from the ILAE Task Force

Seizures are more common in the neonatal period than any other time in life. Most neonatal seizures are acute symptomatic seizures provoked by an underlying brain injury [1, 2]. Neonatal seizures are subclinical or electrographic-only in more than half of seizures, and consequently, EEG is considered the gold standard for the diagnosis [2, 3, 4, 5, 6]. In addition, treating neonatal seizures can be difficult, and a multidisciplinary approach is needed [7, 8, 9].

The International League Against Epilepsy (ILAE) Guidelines in 2005 defined a seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain; this definition did not include electrographic seizures, which are common in neonates [8, 10]. In contrast, the 2013 American Clinical Neurophysiology Society (ACNS) guidelines defined an electrographic seizure in neonates as a paroxysmal abnormal, sustained change in the EEG, characterized by a repetitive and evolving pattern with a minimum two uV voltage and a duration of at least 10 seconds [4]. Brief Rhythmic Discharges (BRDs) are less than 10 seconds discharges that occur in premature and sick neonates. They are associated with seizures in the same or other EEGs and poor outcomes [11, 12]. Although they are not considered seizures according to current definitions, there is ongoing controversy surrounding whether these represent ictal or interictal patterns.

The ILAE defines status epilepticus as a condition resulting from the failure of mechanisms responsible for seizure termination or from initiation of mechanisms, leading to abnormally prolonged seizures [13]. Depending on the type and duration of seizure, it can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks [13]. For neonates, this definition is difficult to apply. ACNS guidelines define status epilepticus as present in a neonate when the summed duration of electrographic seizures comprises >50% of an arbitrarily defined 1-hour epoch [4].

Classifications are clinical tools that aid in the diagnosis, treatment, and management. They reflect current thinking and scientific understanding and develop a common language which is important for a multidisciplinary approach. These need to be updated continually; multiple classifications for neonatal seizures have evolved since Volpe's in the 1970s [14]. The 2017 ILAE seizure classification includes many areas that do not apply to neonatal seizures. For example, certain seizure types do not oc-

cur in neonates, including generalized or bilateral tonic-clonic seizures or absences. Additionally, awareness, cognition, and sensory phenomena cannot be tested. Thus, a new ILAE classification of neonatal seizures has been developed [2].

The new ILAE classification of neonatal seizures uses the same principles and nomenclature as the 2017 ILAE classification, adapted for use in neonatal seizures (see Figure 1). This classification is according to the predominant feature of the seizure rather than the first feature, and all neonatal seizures are considered focal onset. It emphasizes the need for EEG diagnosis and includes electrographic-only (subclinical) seizures. It also includes a new seizure type – sequential seizures (see Table 1).

Diagnosis of Neonatal Seizures by Clinical Signs, Amplitude-Integrated EEG and Conventional EEG

Video EEG plays a central role in the new ILAE Neonatal Seizure Classification. Neonatal seizures are often classified as either clinical seizures, associated with clinical signs which may be subtle, or electrographic seizures, seen on EEG. Electroclinical seizures have clinical signs, accompanied by electrographic seizure patterns on EEG, whereas subclinical seizures are seen only on EEG. Clinical-only seizures are extremely rare in neonates, if they occur at all, possibly when epileptic events are due to deep foci. The vast majority of these 'clinical-only events' are movements not of epileptic origin, mimicking seizures, and can be triggered by stimulation and suppressed by holding the limb [2, 22]. Uncoupling is a common phenomenon whereby electroclinical seizures convert into subclinical seizures, often after administering antiseizure medications [22, 23]. Electroclinical dissociation is rare; this is the inconsistent EEG expression of clinical seizures originating from a deep focus [22, 24].

Most neonatal seizures are subclinical, with no outward clinical signs in 60-80% [22, 23, 25]. This diagnostic challenge was illustrated by Murray et al., in which only one-third of neonatal seizures were clinically expressed, and only one-third of those were correctly recognized by experienced neonatal staff [26]. Only 9% of EEG confirmed seizures were recognized clinically at the bedside. Seizures were also frequently over-diagnosed with inappropriate administration of anticonvulsants; only 27% of clinically suspected seizures had corresponding EEG evidence of seizure activity [26]. Clinical observation is not reliable for diagnosing neonatal seizures.

Amplitude integrated EEG (aEEG) is a processed and time-compressed form of EEG; it offers a method for the diagnosis of neonatal seizures more accurate than clinical observation alone [27]. Bedside caregivers place two or four scalp electrodes, with the processed and compressed aEEG signal shown in multiple hours per screen above the raw EEG tracing showing seconds per screen. Seizures are characterized by an elevation of the upper and lower margins of the aEEG tracing, followed by depression of the upper and lower margin due to suppression of the background following the seizure (See Figure 2). Repetitive seizures cause a saw-tooth pattern on aEEG due to repetitive elevations of the upper and lower margin of the aEEG tracing.

In early aEEG, only one cross-cerebral channel of aEEG was used; however, focal seizures are difficult to identify using this method, as demonstrated by Shellhaas et al. in 2007 [28]. The EEG recording of neonates was downsampled to a single C3-C4 channel for 851 seizures from 125 EEG recordings. 94% of EEGs had at least one seizure visible at C3-C4, and 78% of individual neonatal seizures were visible at C3-C4. Experienced neonatologists identified seizures in 22-57% of the 125 seizure positive records and 12-38% of the 851 individual seizures. Seizures were more likely to be detected if they were of longer duration, higher amplitude, more frequent, visible at C3-C4, and with a more experienced neonatologist [28].

aEEG has important strengths – it is readily available in many NICUs, and background classification is a good measure of global cerebral function, which correlates well with raw EEG background. However, it also has limitations. aEEG is an imperfect diagnostic tool for seizures, and its accuracy is significantly influenced by the skill level of interpretation of the user and the prevalence of seizures [29]. The limited number of electrodes and thus limited brain coverage leads to missed focal seizures [30]. The time-compressed display misses short seizures [27] aEEG is also limited by low specificity, with difficulty distinguishing artifacts such as patting or ECG artifacts from seizures. With aEEG, neonates having seizures can typically be identified; however, seizure burden cannot be accurately quantified, and therefore aEEG is not ideal for guiding therapy accurately [31, 32, 33, 34].

Full array continuous EEG monitoring is the preferred method for diagnosing neonatal seizures. ACNS Guidelines give several indications for conventional EEG (cEEG) monitoring in neonates, outlined in Table 2 [35].

Neonatal seizures have unique features on EEG [36]. These seizures usually start focal and remain well-localized. They can migrate from one hemisphere to the other or alternate between one hemisphere and the other. Seizures most commonly arise from the centrotemporal regions, less often from the occipital, and rarely from the frontal regions [28]. Criteria include a clear onset and offset of rhythmic activity lasting at least 10 seconds, with evolution in location, frequency, morphology, or amplitude [4].

In alignment with the ACNS guidelines, a multicenter consortium prospectively monitored with video cEEG 90 term neonates with HIE undergoing hypothermia. EEG was initiated within the first day of life and continued for at least 24 hours [37]. 48% of these neonates had seizures, including 10% with status epilepticus. Seizures were associated with abnormal initial EEG background (excessively discontinuous, depressed and undifferentiated, burst suppression, or extremely low voltage). However, clinical factors, including pH <6.8, base excess $\leq$20, and 10 minutes Apgar $\leq$3, were not associated with seizures. While clinical factors did not reliably identify those neonates at risk for seizures, the EEG background may be predictive in the first 24 hours [37].

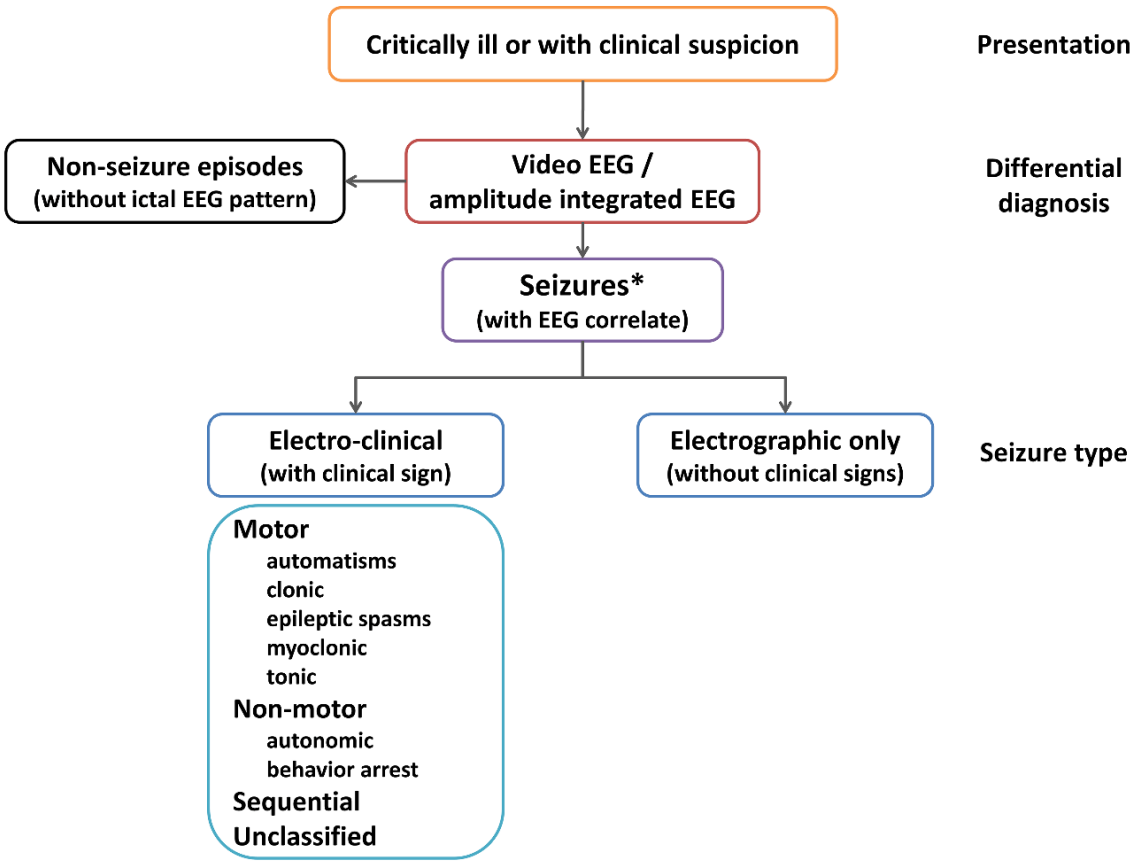

Figure 1. New ILAE diagnostic framework of seizures in the neonatal period, including classification of seizures [2]. *If no EEG is available, refer to the algorithm to determine degrees of diagnostic certainties for neonatal seizures in ILAE guidelines [2].

Treatment of Neonatal Seizures Informed by Current Evidence

The ILAE and WHO released guidelines on the treatment of neonatal seizures in 2011, with four evidence-based recommendations and seven consensus-based recommendations [8]. Clinical seizures should be treated, and electrographic only seizures should be treated in context-specific settings. The first step in treatment is to look for underlying, potentially reversible causes such as hypoglycemia and electrolyte abnormalities and treat them. In specific settings, a trial of pyridoxine should be done. In these guidelines, phenobarbital is the first-line agent for treating neonatal seizures. Second-line agents include midazolam, phenytoin, and lidocaine, with no recommendation regarding the superiority of one of these agents. These guidelines advise that antiseizure medication can be stopped 72 hours after the cessation of seizures [8].

An update to treatment guidelines for neonatal seizures is needed, as significant advances have been made since 2011 with regard to diagnostics with EEG monitoring and treatment advances with therapeutic hypothermia for HIE. Phenobarbital is the first-line agent in this guideline; however, many are resistant to using it, and research is needed to establish alternatives. Bittigau et al. demonstrated the induction of neuronal apoptosis in animal models with phenobarbital [38]. Phenobarbital also leads to electroclinical uncoupling with a decrease in clinical seizures but a relative increase in electrographic seizures [6]. Phenobarbital carries adverse reactions, including respiratory insufficiency and hemodynamic instability with a need for cardiovascular support. Phenytoin is similarly effective as first-line pharmacotherapy in neonatal seizures [39]. However, due to its small therapeutic range, non-linear pharmacokinetics, and the risk of neurological adverse effects, cardiotoxicity, and soft tissue injury with extravasation, it has not been advocated as first-line pharmacotherapy [40].

A proposed alternative to phenobarbital for treating neonatal seizures has been levetiracetam. In contrast to phenobarbital's primary action on the GABAergic synapse, levetiracetam primarily acts on the glutamatergic synapse [41]. Levetiracetam does not induce apoptosis, has a wide therapeutic range, few adverse reactions, and little interaction with other drugs. In a meta-analysis comparing uncontrolled studies of levetiracetam and phenobarbital for neonatal seizures, the efficacy of levetiracetam was 77% as first-line therapy and 63% as second-line therapy [42]. This is in contrast to the efficacy of 43% of phenobarbital in a randomized controlled trial [39]. However, in 2020, Sharpe et al. published a randomized trial comparing levetiracetam to phenobarbital for neonatal seizure treatment [9]. As first-line therapy, neonates were randomized to receive either levetiracetam 40 mg/kg or phenobarbital 20 mg/kg. If seizures continued, they were given an additional 20 mg/kg of levetiracetam or

Table 1. New ILAE classification of clinical semiology in neonates, and related clinical contexts, including etiological considerations.

Semiology		Definition	Clinical context
Motor	Clonic	- Involuntary contractions of muscles or muscle groups - Regularly repetitive jerking	- Possible to diagnose clinically - Common in stroke or other vascular etiologies [1, 15] - Can be multifocal in HIE, infections, etc.
	Tonic	- Sustained muscle contraction - Longer than spasms, lasting seconds to a minute	- Often focal/asymmetric in neonates - Typical for early-infantile developmental and epileptic encephalopathy and other genetic etiologies [15, 16]
	Myoclonic	- Involuntary sudden and brief (<100ms) contractions - Single or multiple with variable topography	- Clinically difficult to differentiate from non-epileptic myoclonus - Typical for early-infantile developmental and epileptic encephalopathy (particularly if due to inborn errors of metabolism) [15] and in preterm infants [17]
	Automatisms	- EEG / aEEG is mandatory - More or less coordinated repetitive motor activity often resembling a voluntary movement - Often oral or manual	- Normal/abnormal behaviors can mimic automatisms - Often a component of seizures in self-limited neonatal seizures
	Epileptic spasms	- EEG / aEEG is mandatory - Sudden flexion, extension, or mixed of proximal and truncal muscles - More sustained than myoclonic but <4sec	- Rare in neonates - May be seen in pyridoxine dependent seizures and other metabolic disorders [15, 18]
Nonmotor	Autonomic	- A distinct alteration of autonomic nervous system function involves cardiovascular, respiration, gastrointestinal, vasomotor, and thermoregulatory functions.	- Rare in isolation
	Behavioral arrest	- EEG / aEEG mandatory Arrest of activity. EEG / aEEG mandatory	- May be part of sequential seizures [19] - Seen in temporal onset [15, 20] Only seen in wakefulness and therefore difficult to capture in neonates, required video EEG may be seen as part of sequential seizures
Either motor or nonmotor	Sequential seizures	- Variety of clinical signs during a given seizure - Sequence of heterogeneous components	- Associated with genetic or metabolic causes [15, 16] - Often seen in self-limited neonatal seizures and KCNQ2/3 encephalopathy [21]
	Unclassified	- Often with a tonic phase Due to inadequate information or unusual clinical features with the inability to place in other categories. EEG / aEEG mandatory.	

Table 2. Indications for cEEG monitoring in neonates, adapted from Shellhaas et al. 2011 [35].

Indication for monitoring	Clinical application
	-Differential diagnosis of abnormal paroxysmal events
Evaluate Electrographic Seizures	-Detection of electrographic seizures in selected high-risk populations (HIE, CNS infection, CNS trauma, ICH, high-grade IVH, congenital heart defects requiring early surgery with bypass, stroke or sinovenous thrombosis, genetic syndromes involving the CNS, inborn errors of metabolism)
Judge the Severity of Encephalopathy	Assessment of background abnormalities during acute neonatal encephalopathy of prenatal or perinatal origin

20 mg/kg of phenobarbital. If seizures continued, the other drug was added on as a second line. Seizure cessation was achieved with the first dose with levetiracetam in 21% versus 70% with phenobarbital. The second dose increased this effect to 28% in levetiracetam and 80% in phenobarbital. Following the add-on of the other drug, the secondary efficacy of phenobarbital was 54%, while levetiracetam was 17%. This study demonstrated greater efficacy of 20-40 mg/kg of phenobarbital than 40-60 mg/kg of levetiracetam. The study design allowing rapid recognition of neonatal seizures and treatment initiation may be responsible for the high response rate to phenobarbital in this study compared to historical data [39]. There were more adverse events in the short term with phenobarbital; however, definitive studies with long-term outcomes are needed [9]. While there is good quality evidence to support the use of phenobarbital as first-line pharmacotherapy for neonatal seizures, the choice of second-line treatment is not informed by evidence. Few studies address the efficacy and safety of second-line pharmacotherapy in neonatal seizures, and uncontrolled trials and observational reports carry a substantial risk of publication bias. Sodium channel blockers (phenytoin, lidocaine) and benzodiazepines (midazolam, clonazepam, lorazepam, and diazepam) have been used as well as levetiracetam [41]. Besides phenobarbital, only phenytoin is licensed for use in neonates. In an observational study, response to midazolam was better than to phenytoin [43]. However, this study included only a small number of patients, and results may have been confounded by a change from phenytoin to midazolam during the ten-year study period. Lidocaine has been used mostly in Sweden and the Netherlands. Like phenytoin, it acts as a sodium channel blocker [41]. It also has a small therapeutic range, and its application requires careful cardiac monitoring. One controlled trial suggests higher efficacy than midazolam in a very small cohort, [6] and numerous observational studies describe an efficacy between 77% and 92% [44, 45, 46].

To update treatment guidelines for neonatal seizures, a working group of neonatologists, epileptologists, neurophysiologists, methodologists, and patient representatives worked together to answer priority questions, including which are the preferred first and second-line treatments for neonatal seizures and how long therapy should be continued, among other questions. A literature search identified 318 articles relevant to these priority questions for the ILAE clinical practice guideline management of neonatal seizures. There is a relative dearth of randomized controlled trials in neonates with seizures. These high-quality studies are difficult to conduct due to the diverse etiologies and demographics of neonates with seizures, difficulty obtaining informed consent, and the need for continuous EEG monitoring to assess eligibility and efficacy. As guidelines are developed, it is important to continue to make context-based management decisions and recommendations.

Management of Neonatal Seizures in Resource-Limited Settings

Diagnosis and treatment of neonatal seizures have special considerations in resource-limited settings. There are significant diagnostic challenges in settings where access to EEG monitoring may be limited. EEG is essential to diagnosing neonatal seizures, as 60-80% of seizures are electrographic only, and electroclinical uncoupling may be exacerbated by therapeutic hypothermia and medications, including phenobarbital [1, 3, 23, 47, 48]. With limited access to EEG monitoring, the level of diagnostic certainty for neonatal seizures drops to a "possible" label based on clinical monitoring alone [5]. Access to video EEG (vEEG) is a major barrier, with vEEG available in only 2% of low-income settings [49].

In settings without access to EEG, only focal clonic or focal tonic seizures can be diagnosed with probable certainty, while seizures with other clinical manifestations cannot be diagnosed with enough certainty, and electrographic seizures cannot be diagnosed. Given this limitation, the true seizure burden in low and middle-income countries (LMICs) may be greatly underestimated. In resource-limited settings, clinical observation of seizure events remains a valuable tool for diagnosis. If clinical events can be provoked by stimulation, or if the events can be arrested by restraint, the events are unlikely to be seizures [1]. In addition to limited access to EEG, LMICs also frequently have a limited supply of antiseizure medications [50].

Management of neonatal seizures in resource-limited settings ideally includes assessing fluid status, glucose, electrolytes, and infections along with treatment of these reversible causes. However, there can be limited access to timely and accurate electrolytes and infection screens results [51]. Without access to continuous EEG monitoring, the care of neonates at risk for or with suspected seizures is focused on symptomatic management in the hope that this will impact seizure occurrence and sequelae. Most treatment protocols include phenobarbital, benzodiazepines, and levetiracetam. In LMICs, both access to airway support for benzodiazepines and access to less-sedating levetiracetam is lacking

[8]. Access to adequate cooling devices for therapeutic hypothermia, the gold standard intervention for HIE, is also limited. Innovative cooling therapy methods are now used in LMICs, including insulated ice caps, water bottles, servo-controlled fans, and frozen gel packs. However, many of these devices lack efficacy, and therapeutic hypothermia is not associated with a statistically significant reduction in neonatal mortality in LMICs [52, 53].

In LMICs, treatable conditions, such as hypoglycemia and infections, should be diagnosed and treated rapidly [51]. Where there is no access to EEG, seizures should be diagnosed clinically when able, recognizing that most seizures will be missed [8]. Improved access to EEG and aEEG is needed, and providers who can interpret them. Existing technology can be leveraged, including video messages and pooled resources.

Conclusion

Neonatal seizures present unique challenges in classification, diagnosis, and treatment and thus, require guidelines distinct from those applied in the care of children and adults. Evidence and consensus-based guidance provide a framework for a common approach tailored to specific settings and individual patients.

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors have made a substantial contribution to conception and design, have drafted the manuscript and revised it critically for important intellectual content, and have given final approval for the version to be published.

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