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Book Review

Electroencephalographic monitoring for seizure identification and prognosis in term neonates

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A B S T R A C T

Seizures represent a manifestation of neurological disease in the neonatal period. Historically, neonatal seizures were identified by direct clinical observation. However, since most seizures are electroencephalographic (EEG)-only (subclinical, non-convulsive) and clinical manifestations may be subtle, many clinicians place increasing importance on EEG data including conventional EEG or amplitude-integrated EEG to identify seizures in neonates. Beyond seizure identification, the EEG is a robust source of information about brain function that can be useful for neurobehavioral prognostication in some neonates. This review summarizes the available data regarding EEG for neonatal seizure diagnosis and brain function assessment.

1. Introduction

Seizures represent a manifestation of neurological disease in the neonatal period. Historically, neonatal seizures were identified by direct clinical observation. However, clinical diagnosis of neonatal seizures is difficult since the clinical manifestations may be subtle. Further, and even more problematically, most neonatal seizures are electroencephalographic (EEG)-only (non-convulsive, subclinical) and have no clinically evident manifestations. Thus, many clinicians place increasing importance on EEG data including conventional EEG (cEEG) or amplitude-integrated EEG (aEEG) to identify seizures in neonates, and recent guideline and consensus statements propose an expanded role for EEG monitoring for seizure identification. Beyond seizure identification, the EEG is a robust source of information about brain function that can be obtained non-invasively at bedside and in a continuous or repeated manner, permitting assessment of change over time. Given these characteristics, the EEG background patterns yield valuable information about brain injury severity and prognostication for subsequent neurobehavioral outcomes. This review summarizes the available data regarding EEG for neonatal seizure diagnosis and brain function assessment.

2. Key definitions and terminology

A seizure is defined clinically as a paroxysmal alteration in neurological function (i.e., behavioral, motor, or autonomic function). This definition includes paroxysmal alterations that are definitely epileptic due to their temporal association with EEG seizure activity, which are referred to as electro-clinical seizures, as well as paroxysmal clinical phenomena that are not consistently time-locked with EEG seizure patterns, which are referred to as clinical-only seizures. It remains unclear how many of these clinical events without identifiable EEG correlates are epileptic and therefore unclear how to best manage them.

The American Clinical Neurophysiology Society developed a report regarding Standardized EEG Terminology and Categorization for the Description of Continuous EEG Monitoring in Neonates [1]. The report defined three types of neonatal seizures: (i) clinical-only seizures in which there is a sudden paroxysm of abnormal clinical change that does not correlate with a simultaneous EEG seizure; (ii) electroclinical seizures in which there is a clinical seizure coupled with an associated EEG seizure; and (iii) EEG-only seizures (also referred to as subclinical, non-convulsive, or occult seizures) in which there is an EEG seizure that is not associated with any outwardly visible clinical signs. The report defined an EEG seizure as "a sudden, abnormal electroencephalogram (EEG) event defined by a repetitive and evolving pattern with a minimum 2 μV voltage and duration of at least 10 seconds." The major EEG correlates of neonatal seizures consist of spikes and/or sharp waves and focal rhythmic discharges, occurring as a distinct change from

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background, and they may spread to adjacent cortical regions or to homotypic areas of the contralateral hemisphere. Further, seizures are classified as having a generalized mechanism of onset or focal mechanism of onset. Focal seizures have a defined region of onset followed by electrical spread within the hemisphere or to the contralateral hemisphere with time. Generalized seizures almost immediately involve bilateral neural networks such that electrical activity appears on both sides of the brain simultaneously on EEG [2]. Most neonatal seizures have onset that is focal or multifocal. Since network connections are not fully developed, spread of the seizure within one hemisphere [3] and secondary generalization to the contralateral hemisphere [3,4] occur less frequently in neonates than in older children.

Whereas a seizure on EEG is comprised of an evolving pattern of epileptiform discharges, not all epileptiform discharges are seizures. Epileptiform discharges, sometimes referred to as “sharp waves” or “spikes”, are brief abnormalities that stand out from the EEG background, usually due to a peaked or sharp appearance. As summarized in the American Clinical Neurophysiology Society's guideline, studies indicate that it is normal for neonates to have some epileptiform discharges (with fewer than one per minute over the central or temporal regions but not over other regions), and many neonates with epileptiform discharges do not experience seizures. However, epileptiform discharges that occur in runs are clustered in one region are associated with an increased risk of seizure occurrence [1]. Brief rhythmic discharges (BRDs) meet the criteria for neonatal seizures (sudden, abnormal, evolving), but are shorter in duration than 10 s. BRDs were formally referred to as BIRDS, but the “I” sometimes stood for “ictal” and sometimes “inter-ictal”, reflecting the uncertain categorization of these events. BRDs are associated with underlying brain pathology and are associated with the occurrence of seizures, as well as an increased risk of future developmental delay, cerebral palsy, and mortality [5,6]. Further, some BRDs are associated with clinical signs including focal clonic activity [5,6] indicating that the exact separation between seizures and shorter rhythmic discharges is indistinct. The 10 s duration of seizures is largely arbitrary, and electrographic events with a clinical correlate are generally considered electro-clinical seizures, even if they last <10 s.

Specific features of the neonatal EEG indicated by the American Clinical Neurophysiology Society's guideline should be evaluated and documented, including the behavioral state, EEG background features (symmetry, synchrony, voltage, variability, reactivity, and dysmaturity, and the presence or absence of normal graphoelements (delta brushes, rhythmic temporal theta, anterior dysrhythmia, and encoche frontales), the presence of EEG transient patterns such as sharp waves and BRDs), and the presence of seizures and status epilepticus [1].

3. Conventional EEG for neonatal seizure identification

Three main problems encountered when diagnosing and managing seizures using clinical observation alone have led to increased reliance on EEG monitoring with either cEEG or aEEG. First, many neonates experience only EEG-only seizures, and EEG-only seizures constitute the majority of neonatal seizures. Since there is no clinical correlate, identification requires cEEG or aEEG. Second, even in neonates with clinically evident electro-clinical seizures, administration of anti-seizure medications may induce electromechanical dissociation or uncoupling in which clinically evident seizures cease but EEG-only seizures persist. Third, clinical events may be difficult to distinguish as seizure or non-seizure based on clinical observation even by skilled clinicians, potentially leading to underdiagnosis of true seizures (thus creating missed opportunities to intervene) or overdiagnosis of non-epileptic events as seizures (leading to unnecessary exposure to anti-seizure medications with potential adverse effects). Each of these problems is discussed below.

A major issue with clinical diagnosis of seizures is the high incidence of EEG-only (non-convulsive, subclinical, occult) seizures in neonates [7–14]. Numerous studies have indicated that about 80–90% of EEG seizures in neonates have no associated clinical correlate, and therefore would not be identified without continuous EEG monitoring even by expert and observant bedside clinicians [3,9,13,15–18]. Clancy et al. evaluated 41 neonates with seizures occurring frequently enough to occur during a routine EEG. Only 21% of 393 seizures identified on EEG were accompanied by clinically evident seizure activity (i.e. electroclinical seizures), whereas 79% were EEG-only seizures. Electroclinical seizures and EEG-only seizures had similar durations, and there were no differences in the degree of encephalopathy [9]. Similarly, Murray et al. evaluated 51 term neonates with cEEG monitoring. Nine neonates experienced a total of 526 electrographic seizures, and only 19% of the electrographic seizure time was accompanied by clinical manifestations. Further, only 9% of electrographic seizures were accompanied by clinical seizure activity that was identified by neonatal staff [15]. These data indicate that most neonatal seizures are EEG-only seizures identifiable only with EEG monitoring.

In neonates with clinically evident seizures, administration of anti-seizure medications may lead to electromechanical uncoupling (or electromechanical dissociation) in which the clinically evident seizures cease but EEG-only seizures persist following the administration of anti-seizure medications [13,19]. In the aforementioned study by Clancy et al. in which 79% of 393 electrical seizures recorded were not accompanied by clinical seizure activity, 88% of the cohort had been treated with one or more anti-seizure medications [9]. Thus, when clinically evident electro-clinical seizures terminate following anti-seizure medication administration, EEG monitoring may be needed to assess for ongoing EEG-only seizures.

Data concerning the development of Cl^- transporters in perinatal human brain provide a rational explanation for electromechanical uncoupling/dissociation. There is a developmental mismatch between the NKCC1 transporter responsible for Cl^- influx and the KCC2 transporter responsible for Cl^- efflux such that neuronal Cl^- levels are likely high in the perinatal brain. GABA activation results in Cl^- efflux with resulting depolarization, and thus excitation. Therefore, administration of anti-seizure medications that are GABA agonists, such as phenobarbital and benzodiazepines, may not terminate electrographic seizures. However, because the maturation of the transporters occurs in a caudal-to-rostral direction, neuronal Cl^- levels in the brainstem and spinal cord motor systems would be expected to decrease to normal levels before cortical neuronal levels [20,21]. Thus, GABA activation induced by anti-seizure medications could eliminate the motor phenomena of the seizure despite the persistence of the cortical electrographic component, resulting in electroclinical dissociation/uncoupling (see Katsarou et al. in this issue).

EEG data may help determine whether clinical events are seizures that could benefit from anti-seizure medication administration or whether they are non-ictal events in which anti-seizure medication administration can be avoided. Some seizures have readily identifiable clinical manifestations (i.e., clonic or tonic components), whereas the clinical manifestations of many seizures are more difficult to identify (i.e., orolingual, ocular, or autonomic components). Problematically, the subtle seizure types that are more difficult to diagnose tend to occur more often than the more readily diagnosed seizure types in neonates. A study of 61 seizures in 24 neonates classified seizures by their most prominent clinical features. Clonic and tonic seizures, which might be more readily

identified, occurred only in 20% and 8% of neonates, respectively. However, oro-lingual, ocular, and autonomic features which might be more difficult to identify were the main features in 55% of neonates [22]. As subtle seizures are frequent occurrences, clinical diagnosis of seizures even by expert and observant bedside caregivers may be difficult and unreliable. One study presented clinical data and video clips of abnormal neonatal movements from 20 neonates to 137 observers, including 91 physicians from seven neonatal intensive care units [23]. Observers classified the movements as seizure or non-seizure. Compared to the reference standard of EEG classification, observers classified events correctly only 50% of the time on average. Further, inter-observer agreement was poor for both physicians and other healthcare professionals. Similarly, in a study of staff observing high-risk neonates, only 9% of 526 electrographic seizures were identified by clinical observation, indicating underdiagnosis of seizures occurred. Additionally, 78% of 177 non-seizure paroxysmal events were incorrectly identified as seizures, indicating an overdiagnosis of seizures [15], which might have led to administration of unnecessary anti-seizure medications with potential risk but without potential benefit.

Given these data, there is increasing emphasis on continuous EEG monitoring to identify and manage seizures in neonates. Many neonatal intensive care units report using EEG monitoring with either cEEG or aEEG, to identify and manage neonatal seizures [24,25]. Additionally, recent guidelines and consensus statements have advocated for a prominent role for EEG monitoring [26–28]. This longer recording is recommended over briefer EEG recordings since many neonates with hypoxic–ischemic encephalopathy will not have seizures in the first hour of recording but will experience electrographic seizures within the first or second day [15,29,30]. Studies in neonates with hypoxic–ischemic encephalopathy indicate that the majority of acute seizures occur within 48–72 h of birth [14,29–32], although the actual timing of the acute brain injury may be unknown or slowly progressive over a period of time. Since EEG monitoring may identify events as non-epileptic, enhanced EEG monitoring and establishment of seizure management protocols may lead to less exposure of neonates to anti-seizure medications. A study evaluating care before and after implementation of a neonatal neurocritical care service found that despite increased use of EEG monitoring and vigilance for seizures, neonates receiving care after the service was established received an average of 30 mg/kg less cumulative phenobarbital and five fewer days of maintenance therapy [33]. Similarly, introduction of a neonatal status epilepticus algorithm led to a reduction in phenobarbital concentrations (57 vs 41 μg/mL) [34].

4. Amplitude-integrated EEG for seizure identification

Amplitude-integrated EEG is in widespread use by neonatologists and some neurologists to identify EEG seizures at bedside without the use of more resource-intense conventional EEG. The technique uses a reduced number of electrodes compared to a conventional EEG recording to generate a single channel (two electrodes and a ground lead) or dual-channel (four electrodes and a ground lead) EEG tracing. The EEG signal is modified and compressed using algorithms which vary slightly between manufacturers to generate the final display showing several hours of aEEG data on a single screen. Electrographic seizures are characterized by upward arches, or a sudden rise in both the upper and lower margins of the trace.

The primary advantages of aEEG relate to its relative ease of use. The limited electrode array can be applied by those without specialized training (i.e., not EEG technologists) and the display can be interpreted by bedside caregivers, generally without involvement of electroencephalographers or neurologists [25]. Due to these advantages and the resource intensity of cEEG monitoring, aEEG is widely used in neonatal intensive care units for seizure identification and management [24,25]. However, one survey reported that only 28% of neonatologists felt confident in their aEEG interpretations [25].

The key question related to aEEG use is how accurately the technique identifies EEG seizures. If the technique does not lead to identification of seizures, then neonates may not undergo needed treatment. By contrast, if the technique leads to overdiagnosis of non-epileptic events as seizures, then neonates may be exposed to unnecessary and potentially harmful anti-seizure medications. A systematic review of aEEG in neonates for seizure diagnosis identified ten studies for inclusion, and half of the studies were considered to have a risk of bias [35]. Despite these limitations, some summary statements were possible. For detection of individual seizures, when aEEG was used with the raw EEG tracing available, the median sensitivity was 76% (range: 71–85%) and the median specificity was 85% (range: 39–96%). When aEEG was used without the raw EEG tracing the results were worse; the median sensitivity was 39% (range: 25–80%) and the median specificity was 95% (range: 50–100%). More experienced clinicians were more accurate. Additionally, seizures that had low amplitude, were of brief duration, or that occurred distant from the aEEG recording sites were less likely to be identified [35]. Overall, the reported studies indicate that reliance on aEEG alone might underdiagnose seizures in some neonates, potentially missing an opportunity to intervene, but might overdiagnose seizures in some neonates, potentially leading to unnecessary anti-seizure medication exposure [16,35–40].

Several factors impacting seizure identification using aEEG are modifiable and may improve accuracy. First, electrode placement affects aEEG sensitivity, with frontal electrode placement decreasing sensitivity by up to one-third compared to central electrode placement [41]. Thus, it is important to place aEEG electrodes centrally rather than over the forehead. One study evaluated 851 seizures from 125 conventional EEG recordings and found that 94% of neonates had at least one seizure visible in the central channel on a single-channel EEG tracing, and that 78% of individual seizures appeared in the central channel which would generally be assessed using aEEG [38]. Thus, there may be a ceiling effect for seizure identification using aEEG recorded from even the central region based on the spatial characteristics of seizures. Second, use of newer aEEG systems with two channels has expanded spatial coverage, which may improve seizure identification related to focal lesions, such as stroke [42,43]. Third, the use of aEEG in combination with review of source EEG, particularly from multiple channels, has been shown to improve sensitivity and specificity in seizure identification [37]. Conventional EEG review may help determine whether the aEEG change appears to be artifactual (which may be higher amplitude than background activity) or rhythmic EEG seizure activity. Fourth, the sensitivity and specificity of aEEG for seizure identification is partially dependent on the experience of the user. Although new aEEG users identify seizures with specificity <50%, experienced aEEG users may achieve sensitivity and specificity of almost 85% [16,35,36,39,40]. Thus, courses and educational tools may enhance aEEG training for physicians and nurses.

Despite the limitations of aEEG, some studies indicate that aEEG improves management in a manner that may yield more favorable outcomes. In a study of 202 neonates, those who underwent aEEG monitoring had greater precision in the diagnosis of neonatal seizures than contemporary controls with fewer seizures diagnosed based on clinical signs alone [44]. Further, more accurate diagnosis of seizures and subsequent management may reduce seizure exposure in neonates. In a randomized study, 33 infants underwent aEEG. Neonatologists viewed aEEG in their routine clinical care for

19 patients, but they were blind to the aEEG data for 14 patients. Among neonates for whom aEEG data were available to neonatologists, there was a trend toward reduced seizure exposure. Further, neonates with lower duration of seizures exhibited less severe brain injury on magnetic resonance imaging (MRI) [45]. Similarly, a prospective single-center study assessed 26 neonates who were randomized to have management guided by clinical data only ($n = 16$) or by clinical and EEG data including cEEG and aEEG ($n = 10$). The group with EEG data used for clinical management had a lower seizure burden and more rapid time to treatment completion. Additionally, neonates with increasing seizure burden had worse MRI injury scores and lower performance on cognitive, motor, and language composite Bayley scores [46]. Thus, despite the imperfections of aEEG, it may be a useful tool to reduce seizure exposure in neonates.

Whereas aEEG is the most used technique for neonatal seizure identification, other quantitative or compressed forms of EEG are also available [47], and combined use of multiple methods may improve accuracy. Development of automated seizure detection techniques may eventually allow for easier and more rapid seizure detection, combining the ease of use of limited-array and quantitative EEG with the full detail of conventional full-array EEG.

5. Guidelines and consensus statements regarding EEG for neonatal seizure identification

The American Clinical Neurophysiology Society published a guideline on continuous EEG monitoring in the neonate in 2011. It was created by a panel of expert electroencephalographers who aimed to standardize care by describing the best EEG monitoring practices in the neonates while recognizing that not all recommendations would be feasible or applicable across institutions. The guideline states that "conventional video-EEG monitoring is the gold standard for neonatal seizure detection and quantification and should be used whenever available for seizure detection and differential diagnosis of abnormal appearing, paroxysmal clinical events. It is the ideal tool to measure the exact number and duration of seizures, their site(s) of onset and spatial patterns of migration." Further, the guideline described four main indications for EEG monitoring. First, cEEG monitoring could be used to determine whether paroxysmal events (sudden, stereotyped, repetitive, unexplained clinical events) are seizures, particularly in patients at high risk for seizures, such as those with acute encephalopathy, cardiac or pulmonary conditions which increase the risk for acute brain injury, central nervous system infections, brain trauma, inborn errors of metabolism, perinatal stroke, sino-venous thrombosis, prematurity with intraventricular hemorrhage and/or low birth weight, and genetic syndromes. Second, cEEG monitoring could be used to identify EEG-only seizures in high risk neonates. Third, cEEG monitoring could be used during the anti-seizure medication weaning period to evaluate for recurrent seizures. Fourth, cEEG monitoring could help assess encephalopathy by tracking EEG background changes over time. The guideline also provides technical recommendations including: (i) electrodes be placed using the International 10–20 system, modified for neonates, with additional electrocardiogram, respiratory, eye, and electromyography leads; (ii) at least 1 h of recording be assessed to adequately assess cycling through wakefulness and sleep; (iii) high-risk neonates be monitored for at least 24 h to screen for electrographic seizures; and (iv) in neonates with seizures, monitoring should continue during seizure management and for an additional 24 h after the last electrographic seizure. The guideline states that aEEG can be a "useful, initial complementary tool," but that conventional EEG remains the gold standard [48]. The World Health Organization published a guideline on neonatal seizures in 2011. It recommended that, in specialized facilities where continuous EEG monitoring is available, all clinical seizures should be confirmed by EEG and all electrographic seizures should be treated, including those without clinical correlate and only identified by EEG [28]. The American Academy of Pediatrics published a Clinical Report in 2014 reviewing neonatal encephalopathy and the use of therapeutic hypothermia, concluding that centers offering therapeutic hypothermia should provide comprehensive care for affected neonates, including seizure detection and monitoring with either conventional EEG or aEEG [27]. It is important to consider that continuous EEG monitoring may not be available at all centers and that transporting some neonates to centers with EEG monitoring capabilities may not be possible due to medical risks inherent in transport or other practical considerations. Each of these guidelines acknowledges that decisions must be made for individual patients with respect to institutional or regional resources.

6. Seizures and outcome

Animal models have demonstrated that seizures in the immature brain have negative impacts on the individual, both acutely and chronically [49]. Clinical data replicating the negative impact of neonatal seizures has been slower to demonstrate these outcomes than animal data, but recent studies consistently indicate that neonatal seizures are associated with less favorable outcomes including higher mortality, more severe neuroimaging abnormalities, more frequent subsequent development of epilepsy, and more frequent occurrence of neurobehavioral impairments. For example, a literature review of 44 studies including 4538 children with a history of neonatal seizures reported that 18% developed epilepsy. Associated neurologic impairments were present in 81%, including cerebral palsy and intellectual impairment in 45%, cerebral palsy alone in 6%, and intellectual impairment alone in 8% [50]. Similarly, a prospective cohort of 88 children (62 term, 26 preterm) with a history of neonatal seizures was followed for a median of 10 years. Both term and preterm neonates had high rates of mortality (16% term, 42% preterm) and disabilities (39% term, 46% preterm). Among term neonates, post-neonatal epilepsy was reported in 18%, learning disabilities in 27%, cerebral palsy in 17%, and intellectual disability in 14%. Among preterm neonates, epilepsy was reported in 40%, learning disabilities in 25%, cerebral palsy in 53%, and intellectual disability in 40%. Predictors of poor outcome among this heterogeneous cohort included the presence of severe encephalopathy, cerebral dysgenesis, complicated intraventricular hemorrhage, infections in preterm neonates, abnormal EEG, and the requirement of multiple anti-seizure medications [51] (see Glass et al. in this issue).

In studies with univariate analysis of seizure occurrence and outcome, it is unclear whether seizures cause secondary brain injury, thus worsening outcome, or whether seizures serve as biomarkers of more severe underlying brain injury, resulting in unfavorable outcomes. It is therefore important to adjust for the underlying brain injury etiology and severity. Several studies with multivariate adjustment for variables indicating brain injury severity demonstrate that seizures are associated with unfavorable outcomes [30,52–54]. As a first example, a multi-center prospective study of 85 full-term neonates with moderate–severe hypoxic–ischemic encephalopathy treated with therapeutic hypothermia while undergoing aEEG identified seizures in 52% of the cohort. The aEEG background and MRI were assessed for severity using standardized scoring systems. On multivariate analyses, high seizure burden was associated with a severe pattern of MRI injury (odds ratio (OR): 5; 95% confidence interval (CI): 1.47–17.05; $P = .01$) [30]. As a second example, a prospective study of 77 full-term neonates with hypoxic–ischemic encephalopathy

assessed seizure burden and brain MRI injury severity. After adjustment for MRI severity of hypoxic–ischemic brain injury, every point increase in the seizure severity scale was associated with a 4.7-point reduction in intelligence quotient. The median intelligence quotients for neonates with no seizures, mild/moderate seizures, and severe seizure burdens were 97, 83, and 67, respectively. After MRI severity adjustment, the seizure severity score was also associated with an increased odds of an abnormal neuro-motor score (OR: 20; 95% CI: 3–140) [52]. As a third example, a multi-center prospective cohort of 49 full-term neonates with moderate to severe hypoxic–ischemic encephalopathy treated with therapeutic hypothermia was monitored with aEEG and found seizure occurrence in 59% of neonates. Seizure burden, aEEG background, and MRI severity were assessed. Multivariate analysis showed an association between high seizure burden and severe MRI injury with an odds ratio of 4.2 for severe MRI injury with high seizure burden (95% CI: 1.01–17.5; $P = .05$). Additionally, aEEG background at 24–48 h showing discontinuity was associated with an increased risk for more severe MRI injury. Thirty-three percent of the cohort had poor neurodevelopmental outcomes assessed using the Bayley Scales of Infant Development, and this was associated with severe MRI injury [53].

Several studies have demonstrated that identification and management of neonatal seizures using EEG data reduce seizure exposure, and that lower seizure exposure is associated with more favorable outcomes. One study evaluated 33 neonates with hypoxic–ischemic encephalopathy who all underwent aEEG but who were randomized so that neonatologists could view aEEG in their routine clinical care for 19 patients but were blind to the aEEG data for 14 patients. When the two groups were combined, neonates with lower duration of seizures exhibited less severe brain injury on MRI. Further, mortality was higher among neonates with a higher seizure burden (428 min in those who died versus 164 min in those who survived [42]. As described above, a second study of 69 neonates with hypoxic–ischemic encephalopathy were all monitored with continuous EEG but randomized to treatment of only clinically evident seizures versus treatment of electrographic seizures. Higher seizure burden across the entire cohort was associated with more severe MRI injury scores ($P < .03$) and lower scores on Bayley Scales of Infant Development (cognitive composite: $R = 0.502$, $P = .03$; motor composite: $R = 0.497$, $P = .01$; language composite: $R = 0.444$, $P = .03$) [46].

7. EEG for outcome prediction

Predicting neurobehavioral outcome is best approached using a multi-modal strategy incorporating clinical, examination, neuroimaging, and EEG data. The potential value of EEG information lies in the facts that: (i) it can be obtained early in the course at bedside and repeated over time, which may be more difficult with neuroimaging; and (ii) it is objective and directly assesses brain function. Thus, the EEG background may be useful in predicting outcome in individual patients, and greater focus has been placed on the ability of the EEG background to add prognostic information, bearing in mind the limited predictive abilities of clinical data [13,55]. However, when using EEG for prognostication and particularly with decisions regarding withdrawal of technological support, it is important to remember that evaluations of neonatal EEG findings are sometimes difficult and that interpretation may vary even among experienced electroencephalographers [56,57]. Recent standardized terminology has been proposed by the American Clinical Neurophysiology Society [1], and this standardization of neonatal EEG background patterns should decrease variability in neonatal EEG interpretation, allowing for more reliable prognostication based on the results. In several careful studies, the background EEG pattern was found to correlate especially well with outcome in both full-term and premature neonates with seizures. Most neonates with seizures occurring on a normal EEG background generally have a normal outcome, whereas 90% of neonates with seizures on an abnormal EEG background (e.g., attenuation in voltage, burst-suppression, or excessive discontinuity) have an abnormal outcome. Moderate background abnormalities, which generally account for about 15–30% of the tracings, are associated with an intermediate likelihood of sequelae [58].

Data on the ability of the neonatal EEG background patterns to predict neurobehavioral outcomes are most readily available for neonates with hypoxic–ischemic encephalopathy. However, even in this more homogeneous group, EEG patterns and outcome measures are variably defined in the literature. Overall, normal EEG background, particularly in the first day of life, is associated with normal outcomes in 80–100% of neonates, burst-suppression background is associated with unfavorable outcome in 80–100% of neonates, and an attenuated EEG background is associated with unfavorable outcome in 90–100% of neonates. A systematic review of the predictive ability of neonatal EEG background features for neurodevelopmental outcomes at age $\geq$12 months assessed 31 studies with 1948 term neonates with hypoxic–ischemic encephalopathy monitored with EEG and aEEG from 1960 to 2014 [59]. Therapeutic hypothermia was used in only 23% of neonates. Severely abnormal EEG tracings in the neonatal period (burst-suppression, low voltage, and flat EEG tracings) were the most accurate predictors of poor neurodevelopmental outcomes, with a pooled sensitivity of 0.87 and pooled specificity of 0.82 for burst-suppression, a pooled sensitivity of 0.92 and pooled specificity of 0.99 for low-voltage patterns, and a pooled sensitivity of 0.78 and pooled specificity of 0.99 for flat tracings.

There are several important caveats to consider. First, caution must be used in attributing a grave prognosis to abnormal paroxysmal patterns with long silent periods in premature neonates, since they can have more discontinuous patterns and since substantially fewer outcome data are available. Second, it is key to consider the possible impact of sedating medications on the EEG background. Some neonates with backgrounds that predicted unfavorable outcome, yet had favorable outcomes, may have had their backgrounds worsened by phenobarbital. Third, since EEGs may evolve over time, repeat EEG tracings may be useful. Although the most predictive timepoint of a neonatal EEG has not been identified, EEG abnormalities which persist are more predictive of unfavorable outcomes [60]. The worsening of a background or development of an abnormal background also predict unfavorable outcomes [61]. For these reasons, a single EEG is not recommended, and either continuous EEG or serial routine EEGs may be needed.

8. Conclusions

The use of EEG monitoring in the neonatal population is evolving and increasing since the EEG offers a unique window into the cerebral health of the neonatal brain. Given that prolonged and repetitive seizures in the neonatal period are associated with unfavorable neurobehavioral outcomes and mortality, a primary target of EEG monitoring remains seizure identification. Additionally, assessment of the neonatal EEG background offers prognostic information. Future work is necessary to improve quantitative EEG methodology so that EEG data are more readily accessible to the bedside clinician. Additionally, future research is needed to refine the prognostic ability of EEG data when applied to individual neonates, in order to provide prognostic information or to stratify patients by early brain injury severity for subsequent neuroprotective trials.

8.1. Practice points

- Seizures are the most frequent manifestation of neonatal brain injury.
- EEG monitoring is essential for accurate identification of neonatal seizures because: (i) clinical seizure identification is difficult since the clinical manifestations may be subtle, leading to missed seizures; (ii) unusual clinically evident events may not be seizures, leading to overdiagnosis of seizures; and (iii) most seizures are EEG-only, without any clinical correlate.
- Continuous conventional EEG monitoring is the reference standard for neonatal seizure identification, but it is labor intensive, expensive, and requires the expertise of an electroencephalographer. Thus, quantitative EEG analyses such as aEEG are often used, albeit imperfectly, if conventional EEG is not feasible.
- There is growing evidence that the neonatal EEG can be utilized for both acute and chronic neurobehavioral prognostication. Whereas individualized patient prediction has not yet been perfected, the presence of specific EEG background patterns and/or the acute seizure burden provides predictive information, which can be informative for early clinical decision-making and setting familial expectations.

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