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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

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