EEG and the newborn

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Abstract. Despite the evolution of new technologies for assessing neonatal brain function, electroencephalography (EEG) remains a powerful tool for neurodiagnostic and prognostic purposes in neonates. It is considered the gold standard for distinguishing epileptic seizures from non-epileptic paroxysmal events and for detecting subclinical seizure activity in high-risk babies. In those babies severely ill, EEG is even more efficient as a predictive test than the neurological examination. The prognostic value of neonatal EEG has been long recognized in term as well as in preterm infants. Background patterns, more than patterns of ictal discharges, correlate significantly with the long-term outcome. Although most abnormalities on the neonatal EEG are nonspecific, certain patterns can be highly suggestive for diagnosis. Prognostic value can be increased by obtaining early recordings, possibly within the first 48 hr of life, prolonged recordings to include samples of different activity states, and serial EEGs at short intervals to assess rapid changes that are likely to occur in high-risk infants. It is important to distinguish neonatal seizures from neonatal-onset epilepsies and epilepsy syndromes. Both benign and malignant neonatal epilepsy syndromes exist. While benign familial neonatal seizures represents a neonatal syndrome with benign outcome, early myoclonic encephalopathy and Ohtahara syndrome are the earliest form of age-dependent severe epilepsy syndromes. Early myoclonic encephalopathy and Ohtahara syndrome are both characterized by the presence of a burst-suppression EEG pattern. This pattern is usually associated with a poor prognosis and is considered the electroencephalographic correlate of a complete disconnection within the thalamocortical systems. Migrating partial seizures in infancy is a newly recognized epilepsy syndrome whose onset can be in the neonatal period. It is characterized by multifocal intractable seizures associated with psychomotor impairment. No etiology has been found so far. Different drugs currently used in neonatal intensive care unit, especially if in the toxic range, can alter the EEG background. Those effects need to be taken in account in the interpretation of neonatal EEG.

Keywords: EEG, newborn, epilepsy, seizures

1. Introduction

Electroencephalography (EEG) is one of the oldest, yet most valuable, diagnostic and prognostic test in neonates. It has been used for decades to objectively assess the neurological status of critically ill neonates and may provide objective evidence for abnormal cerebral functioning following perinatal depression. It represents an important component of the clinical assessment of newborns with neurologic disorders, since it can provide an important extension to the clinical evaluation and should always be interpreted with the awareness of the gestational age of the child. It is considered the gold standard for seizures detection and quantification and for assessment of cortical activity. In critically ill newborns, EEG is even preferable to neurological examination, as their clinical repertoire is narrow, making the neurodevelopmental examination of rather limited value [1,2]. While brain-imaging techniques developed over the last decades have revolutionized the diagnosis of major structural disorders of the neonatal brain, neurophysiologic studies provide continuous documentation of brain function, with or without demonstrable structural correlates. EEG recording
can detect seizures, with or without clinical manifestations, and especially if combined with video monitoring, it can differentiate them from paroxysmal non-epileptic events in order to avoid unnecessary treatment and to institute the correct treatment when required [3, 4]. However, in the pediatric setting, this tool is not always available, as it requires interpretation by a neurologist with expertise in neonatal EEG. These reasons have led to the development of complementary types of cerebral function monitoring, such as amplitude-integrated EEG, which is intended to be applied and interpreted independently by neonatologists in order to allow a real-time interpretation of results. Nevertheless, EEG is necessary if precise classification into normal or mildly, moderately, or markedly abnormal backgrounds is desired, and it can be particularly helpful in the newborn intensive care unit in identifying infants suitable for neuroprotective strategies and allowing accurate diagnosis and stratification of encephalopathy, a prerequisite for the evaluation of results of neuroprotective strategies [5,6].

2. Technique

For the proper assessment of neonatal EEGs, it is mandatory to record at least a phase of active sleep and quiet sleep. In infants less than 30 weeks of conceptional age who spend most of their time in indeterminate sleep, a record of approximately 40 min duration comprising the most continuous and the most discontinuous pattern may be practically sufficient [7]. The EEG in the neonatal period should be performed allowing some stimulations and in an environment as quiet as possible.

There are several technical considerations when recording from a neonatal scalp. High skin resistance impedes low-resistance scalp-to-electrode contact. The minimum standard required includes at least ten scalp electrodes placed following the 10–20 International System of Electrode Placement, modified for neonates (Fig. 1) as well as non-cerebral channels. Whereas the classification of sleep states was developed mainly on the EEG patterns in adults, poligraphic recording became the gold standard for state classification and developmental physiology in the newborn. Therefore, the EEG recording in the newborn should always be a poligraphy that means a continuous and simultaneous recording of cerebral electrical activity, eye movements’ electrooculogram, muscle activity [electromyography (EMG)], heart activity (electrocardiogram) and respiratory activity. Respiratory monitoring should include two respiratory monitors: a thoracic strain gauge or motion transducer to detect chest wall movements in one channel, and a thermistor to detect airflow in the other channel. EMG should include a submental EMG activity monitor. Such monitoring assists in the identification of specific segments of the EEG sleep cycle and, especially if used together with high-synchronized video, facilitates the characterization of seizures by correlating the clinical manifestations with the ictal electrical discharge. Concordance between electrographic and polygraphic signals marks the maturation of the central nervous system (CNS), as reflected in EEG sleep development. Non-cerebral physiologic parameters may also be relevant to the clinical problem that prompted the request for the EEG study, such as apnea. Important sources of artifact can be identified more readily or eliminated by using non-cerebral monitors. As with adults, physiologic and non-physiologic artifacts must be properly identified in neonatal recordings because the may interfere with the interpretation of cerebral activity. The technologist should not only try to identify the source of the artifact but eliminate such artifacts during the recording. Accurate description by the technologist may help the neurologist in the diagnosis of a neurologic disorder in the neonate. It is important to annotate the tracing with particular attention to the state of activity (awake or asleep), to the presence and type of eye movements, facial movements, sucking, crying, and any other events [7].
3. Indications

There are no indications for systematical recording of every newborn in the intensive care unit. However, an EEG should be considered when questions arise regarding the baby’s abnormal neurological status or the possibility of seizures. For instance, EEG will be required for diagnosis of abnormal movements, autonomic signs (i.e. unexplained apnea, flushing of the face), abnormal neurological status (i.e. lethargy or hyperactivity), or reported fetal distress. In those cases, EEG may allow recognition of patterns suggestive of specific conditions such as inherited errors of metabolism or herpetic encephalitis, to detect focal abnormalities like in hemorrhagic or ischemic stroke or abscess, or to identify ictal discharges [8]. Serial studies more accurately document normal ontogeny or the evolution of encephalopathic changes than do single recordings. The continuous changes that occur during early brain development are often associated with striking changes in EEG pattern over short periods. Indeed, EEG patterns are expected to change according to the gestational age. A trained interpreter of neonatal EEG can estimate the electrical maturity of the neonatal brain with an accuracy of 2 weeks of the gestational age for preterm infants and 1 week for full term infant [8,9]. In fact, CNS development of the immature brain in postnatal environment proceeds at about the same rate as during fetal development and evolving electrical patterns reflect the conceptional age of the infant independently of his birth weight. Concordance between electrographic and polygraphic components of EEG sleep begins as early as 30 weeks of estimated gestational age and is complete after 36 weeks of estimated gestational age. The EEG also changes with behavioral state cycles that show an increasing organization with advancing conceptional age [10].

4. Prognostic value

It is generally accepted that the background EEG is a good prognostic tool in preterm infants as well as term infants [11–16]. The EEG features used for prognostic purposes differ among authors. For prognostic purposes, serial EEG recordings are more useful than a single recording [17]. Usually, various features are grouped into different severity grades and correlated with outcome [13]. Some authors use some selected features such as discontinuity measures [18,19], maturational features [20,21], or sharp waves transient [22]. In the newborn with an acute hypoxic insult, the prognostic value of the EEG strongly depends on the day of recording [17]. The longer the time between the hypoxic event and the pathologic tracing, the worst the prognosis. Conversely, EEGs obtained shortly after the insult must be viewed with caution and a follow-up study is highly recommended.

The relationship between neonatal EEG findings and neurological outcome has been investigated in preterm infants younger than 33 weeks of gestation by Watanabe et al. [15]. These authors defined changes in continuity, frequency, and amplitude as acute stage abnormalities, and changes in maturity and waves forms as chronic stage abnormalities. They also used the EEG to assess the timing of brain insult suggesting that acute stage abnormalities in EEG immediately after birth may have originated from insults occurring just before birth. In their study, the absence of chronic stages abnormalities was associated with a favorable outcome in 88%, while dysmature pattern was associated with mental retardation or borderline outcome in 68%. Whereas mildly disorganized patterns were associate with normal outcome in 52%, severely disorganized patterns were associated with moderate or severe CP in 79% of cases [15]. Also, serial EEG recordings beginning immediately after birth demonstrated to be particularly useful to assess the timing and the degree of brain injuries and to elucidate their pathogenesis in young preterm infants [15].

The potential of neuroprotective therapies, such as hypothermia, has raised the importance of accurate prediction of outcome in the first 6 hr of life [6,23,24]. EEG remains our best method of predicting neurologic outcome in hypoxic ischemic encephalopathy [11,12,14]. A normal or mildly abnormal EEG in the first 24 hr of life has a positive predictive value of 94% in predicting a normal neurologic outcome. In contrast, a severely abnormal or inactive EEG predicts death or severe disability in the great majority of cases. Moderate abnormalities will be associated with neurologic disability in 60% of cases. Sarnat scoring has a good predictive value, but cannot be assessed until 24 hr of age, too late for benefiting from currently available neuroprotective therapies. In contrast, EEG grading can be assigned soon after delivery and offers more reliable prognosis than the Sarnat score alone [12,25] Early amplitude-integrated EEG has been shown to accurately predict the severity of encephalopathy and long-term neurologic outcome [26]. For this reason, this tool has been used in the recruitment of infants with moderate and severe encephalopathy to clinical trials of neuroprotecti-
tive hypothermia, giving promising results [23]. However, amplitude integrated EEG shows poor reliability compared with continuous EEG when reported by inexperienced personnel, and does not allow localization of pathology or seizure activity [27].

While most neonatal EEG patterns are nonspecific, the EEG may be the first test to guide the clinician in reaching an unsuspected diagnosis. For example, an interhemispheric or regional asymmetry of background pattern is often the first clue for underlying lesion, such as a prenatal ischemic event, unsuspected by history or examination. Several EEG features may suggest dysgenetic brain anomalies, inborn errors of metabolism, such as non-ketotic hyperglycinemia and pyridoxine dependency, CNS infections like herpes simplex virus encephalitis. In the context of ictal disorders, the EEG has been shown to be an excellent predictor of outcome by the vast majority of prospective or retrospective investigations performed during three decades. Many authors reached the conclusion that, for prognostic purposes, the background EEG patterns are more significant that the patterns of EEG discharge. In a study of 137 full-term infants with neonatal seizures, Rose and Lombroso [28] found that neonates with seizures who had a normal EEG had an 86% chance of normal development at age 4 yr. Conversely, in neonates with low amplitude, periodic or multifocal spikes in the interictal EEG background had only a 7% chance for normal development. Monod et al. [29] found similar correlations for neonates presenting with seizures. In a review of 691 EEGs performed in 270 mostly term-born neonates recorded in the first month of age, they showed that normal EEGs were highly correlated with favorable outcome, while low-voltage, inactive, or burst-suppression EEGs were highly prognostic of poor outcome both in preterm and full-term infants. In another study, Rowe et al. [30] supported these findings in 74 full-term and preterm neonates with seizures, emphasizing that EEG background was more predictive of outcome than interictal sharp waves.

Normalization of a previously abnormal pattern may indicate a minimal impact of a brain insult on maturation. Conversely, progressive deterioration of previously normal or moderately abnormal patterns favors the possibility of long-term neurological sequelae. Repeated recordings provide the clinician with greater predictive information than those derived from a single EEG [31]. However, some EEG patterns are so severely abnormal that they are considered sufficient for the formulation of the prognosis, without the need for serial tests. Some authors feel that predictions can be accurately be advanced when the initial EEG shows an inactive or isoelectric pattern or a burst-suppression pattern, even if the test is obtained shortly after birth [11,28,29]. In order to diagnose an isoelectric pattern, most authors require the absence of all discernible cerebral electrical activity recording at a sensitivity of 2 µV/mm [32]. The technical requirements for the diagnosis of isoelectric recordings in neonates are the same as in adults, namely, using the highest gains, long time constants, and long interelectrodes distances, and meticulous attention to artifacts. An isoelectric pattern is most commonly seen following severe asphyxia, circulatory collapse, and massive intracerebral hemorrhages. It can also be seen in severe malformation of the brain, such as hydranencephaly or massive hydrocephalus. In the absence of drug intoxication, acute hypoxemia, hypothermia, and postictal state, this EEG pattern carries a poor prognosis: most neonates with isoelectric EEG either die in the neonatal period or suffer severe neurologic deficits [11]. Very rarely in the newborn, EEG activity may return normal after an isoelectric EEG recorded in the first 24 hr following an acute hypoxic-ischemic event. Usually, in the survivors, the isoelectric EEG is followed by other abnormal patterns, particularly low-amplitude or burst-suppression backgrounds [33].

Burst suppression pattern on the neonatal EEG is usually associated with a poor outcome. This pattern is characterized by burst of high voltage activity (75–200 µV) lasting 1 to 10 sec with mixed features (spikes, sharp waves, theta, delta) but no age-appropriate activity, alternating with periods of marked background attenuation (voltage < 10 µV) lasting 2 to 45 sec. This periodic pattern is persistent throughout awake and asleep states, unreactive and unaltered by exogenous stimuli (Fig. 2).

Steriade et al. [34] have investigated the cellular correlates of EEG burst-suppression patterns in animals. In this study, burst-suppression was elicited by the administration of an anesthetic agent. About 95% of cortical cells entered burst-suppression, in close time relation with EEG activity, displaying sequences of phasic depolarizing events associated with bursts of EEG waves and an electrical silence of the neuronal membrane during flat EEG periods. In contrast with cortical neurons, only 60–70% of thalamic cells ceased firing before overt EEG burst-suppression and was completely silent during flat periods of EEG activity, while the remaining 30–40% showed intrinsic pacemaking properties discharging rhythmic (1–4 Hz) spike bursts during periods of EEG silence. However, with the deepening of burst-suppression, when silent
Fig. 2. Burst-suppression pattern in a 3-day-old full-term newborn. An alternating pattern of high-voltage mixed frequency activity and voltage attenuation indicates severe diffuse cerebral dysfunction. The bursts contain no age-appropriate activity. The muscle activity over the deltoids and the irregular respiratory pattern differentiate the awake (A) from the sleep (B) state, while the cortical activity with the burst-suppression pattern is invariant.
Fig. 3. Tracé alternant during quiet sleep in a 10 days old full-term infant. This pattern is reactive to stimuli, and alternate with the continuous pattern of the active sleep. It can be distinguished from the burst-suppression by the presence of high-voltage slow wave activity that alternate with period of low voltage activity. The low voltage activity of the trace alternant is higher compared with the interburst activity of the burst-suppression pattern.

EEG periods became longer than 30 sec, thalamic cells also ceased firing. The assumption that full-blown burst-suppression is achieved through virtually complete disconnection in brain circuits implicated in the genesis of the EEG is corroborated by the revival of normal cellular and EEG activities after volleys setting into action thalamic and cortical networks. A recent study demonstrated that a predominant interburst interval duration of more than 30 sec correlated with the occurrence of both unfavorable neurologic outcome and subsequent epilepsy, suggesting that the interburst duration, an easily quantitated EEG parameter, could be valuable for the early estimation of neurologic prognosis in those patients [35]. According to this study, an infant whose EEG contains a predominant interburst interval duration of more than 30 sec has a 100% probability of experiencing severe neurologic disabilities or death and an 86% chance of developing subsequent epilepsy. Burst-suppression pattern has been observed in individuals with cerebral conditions disconnecting the cortex from deep structures. Highly discontinuous pattern as seen in burst-suppression can result from brain immaturity, extensive brain damage or dysfunction. Such dysfunction may be only temporary or be long lasting when structural lesions or diffuse changes of metabolic origin have taken place. Transient EEG burst-suppression is seen in barbiturate anesthesia and hypoxic-ischemic encephalopathy, while a persistent burst-suppression is observed in deep brain tumors, severe congenital metabolic disorders such as non-ketotic hyperglycinemia, or extensive brain malformation such as hemimegalencephaly [36].

The burst-suppression pattern is easy to differentiate from the discontinuous features normally seen during non-rapidly eye moved or quite sleep in infants above 34–36 weeks corrected age, when trace alternant begins to emerge clearly. The discontinuous pattern of trace alternant is distinguished from burst-suppression by the presence of its interburst activity, by being reactive to stimulations, and by the presence of normal EEG features for corrected ages (i.e., delta brushes, temporal theta, or frontal sharp transient), whereas there is also cycling of the discontinuous pattern with the continuous one of the rapid eye movement sleep (Fig. 3). Problems may arise in diagnosing burst-suppression in preterm infants less than 33–32 weeks, because of the trace discontinue that normally occurs at ages that are more immature. The most reliable clue to distinguish the pathological pattern of burst-suppression from the normal pattern of trace discontinue is the clear knowledge of the infant’s conceptional age. Therefore, trace alternant and trace discontinue are two patterns of dis-
continuity that are normal for some conceptional ages but may be abnormal for others, while burst-suppression is usually invariant and lack other features characteristic for the EEGs of neonates of various conceptional ages. Testing for reactivity, usually absent in burst-suppression, is also helpful. Nonetheless, in young preterm infants, serial recording are advisable before formulating the poor prognosis associated with burst-suppression. If such activity is persistent through repeated recordings, invariant and unresponsive to stimulation, with prolonged interburst intervals, then such a pattern may be considered equivalent to the pathologic burst-suppression seen at term, as suggested by Tharp et al. [37] in 1981.

5. Seizures

Normal neonates commonly exhibit a variety of paroxysmal movements including nonconjugate eye movements, sucking movements without associated eye abnormalities, and sleep-related myoclonus. These
normal behaviors as well as pathologic conditions can be difficult to distinguish from epileptic seizures, which can also have somewhat subtle manifestations. EEG is a necessary tool in distinguishing among these entities. In a study of EEG diagnosis of seizures in neonates, 90% of abnormal movements suspicious for seizures were found to be nonepileptic on EEG recording [1].

The EEG should therefore be recorded at the beginning of the first symptoms, and, if possible, before any seizure treatment. Epileptic seizures are most frequent in the neonatal period than in any other time of the life [38,39]. A generally accepted definition of what constitutes an ictal discharge has not been established, especially in the newborn. Most authors classify a discharge as ictal if it lasts at least 10 sec. However, documented clinical and electrical seizures have been described in neonates as lasting only a few sec, while with increasing age seizure activity becomes usually longer in duration. There are striking differences between seizures in neonates and those of older patient in ictal EEG patterns and their correlation with clinical symptoms and pathology [13,40]. Neonates more often have brief albeit recurrent seizures with a brief interictal interval, as opposed to a single prolonged ictal event as
observed in older infants. Seizures may have an erratic evolution, shifting from one area to another even in the presence of a diffuse pathological process (Fig. 4). Just as seizures differ between neonates and older populations, so does status epilepticus [41]. Data from Morton et al. [42] showed that, while neonates with status epilepticus presented with brief, partial, serial seizures with multiple foci, infants older than 2 months of age were capable of having prolonged seizures with typically one focus and possible secondary generalization.
In the newborn, seizures are unique because the neonatal brain differs in both structure and physiology from those of older children and adults. Although the basic organization of the cortex is in place, dendritic growth, axonal-dendritic connections, and synaptic stabilization are not complete in the newborn [43,44]. Likewise, myelination is immature, preventing the rapid well-organized spread of epileptic discharges [45]. Therefore, newborns may present with focal ictal discharges in metabolic disorders (i.e. in hypocalcemic or hypoglycemic seizures) as well as structural lesions (i.e. ischemic stroke). However, in localized structural lesions, seizures tend to be more consistently confined in the affected region even in the case of prolonged or recurrent event (Fig. 5). From a clinical point of view, a seizure may be defined as a paroxysmal alteration in neurological function, i.e. behavioral, motor, and/or autonomic function, associated temporally with EEG seizure activity (electro-clinical seizure). In some occasions, this correlation is lacking (clinical seizures without EEG correlate) but it is not clear whether these latter phenomena are related to an epileptic condition [46–49]. Mizrahi and Kellaway [48] in 1987 suggested classifying as epileptic seizures only those paroxysmal events associated with concurrent electrical seizure activity (electro-clinical seizure). In some occasions, this correlation is lacking (clinical seizures without EEG correlate) but it is not clear whether these latter phenomena are related to an epileptic condition [46–49]. Mizrahi and Kellaway [48] in 1987 suggested classifying as epileptic seizures only those paroxysmal events associated with concurrent electrical seizure activity. However, the inconsistent electrographic capture on the scalp recordings may depend on seizures arising from foci deep within the brain, only inconsistently discharging through final anatomic pathway. Conversely, an electrical seizure without clinical correlate may be the result of a discharge arising from an area of the cerebral cortex, which does not express itself overtly in the newborn, such as a sensory, or language area. However, these considerations should not detract from the use of EEG as the standard means for determining the presence of seizures before consideration of drug treatment. As it can be difficult to distinguish epileptic from non-epileptic seizures, EEG may provide a more accurate endpoint than clinical observation in assessing treatment efficacy [4].

On the other hand, electrical seizures without clinical correlate are frequently recorded, particularly in severely ill newborns, with severe brain damage, or in those who are pharmacologically paralyzed [39]. In one study, only 21% of neonates had a clinical correlate during electrographic seizures [3]. Another report found that only 45% of preterm and 53% of full-term neonates demonstrated clinical signs coincident with their electrographic seizures [50]. This electroclinical dissociation can also be seen after anti-epileptic drugs (AEDs) treatment, particularly phenobarbital. Recently, Scher et al. [4] performed a prospective study on the phenomenon of uncoupling in 59 neonates with electrically confirmed seizures. Uncoupling EEG-clinical seizures was defined as the persistence of electrographic seizures despite the suppression of ≥ 50% clinical
seizures after phenobarbital or phenytoin administration. The uncoupling was noted in 58% of the neonatal cohort. Phenobarbital and phenytoin resulted in equal rate of uncoupling. Therefore, continuous EEG monitoring during treatment of neonatal seizures is advisable in order to assess the efficacy of the treatment [4].

6. Neonatal epilepsy syndromes

It is important to distinguish neonatal seizures from neonatal-onset epilepsy syndromes [51]. An epilepsy syndrome is defined by the combination of age at onset, seizure types, interictal and ictal pattern and, when known, etiology. This concept, developed four decades ago by Gastaut [52] and the School of Marseille, and established by the International League Against Epilepsy (ILAE), remains the gold standard for diagnosis in pediatric epileptology [53]. The recognition of epileptic syndromes allows an accurate diagnosis and management of seizure disorders, and it is useful for research regarding treatments and etiologies, including the genetic ones. The identification of new syndromes is based mainly on clinical and EEG criteria, and advances in neuroimaging and genetics have by no means contradicted this concept [54]. However, most neonatal seizures are provoked seizures, rather than a true epilepsy syndrome, and despite the high prevalence of neonatal seizures, epileptic syndromes in neonates are rare but often overlooked. Currently, four epilepsy syndromes with onset in the neonatal period are recognized by the ILAE [55]: benign familial neonatal seizures (BNFS), early myoclonic encephalopathy (EME), Ohtahara syndrome (OS), also known as early infantile epileptic encephalopathy, and the newly recognized syndrome of migrating partial seizures in infancy (MPSI) [56].

BNFS is a benign neonatal epilepsy syndrome classified among the autosomal dominant focal epilepsies and characterized by onset of seizures during the neonatal period, normal neurologic examination, and negative evaluation for another etiology of the seizures, normal developmental and intellectual outcome, and positive family history of newborn seizures with benign outcome [57–61]. Seizures usually occur in clusters for a few days and then stop after several weeks or months. Seizures are generally brief, lasting for approximately 1 to 2 min, but may occur as many as 20 to 30 times a day. Although generalized seizures have also been reported, seizures are often of a mixed type, starting with tonic posture, apnea and other autonomic features, and progressing to focal or multifocal clonic seizures. EEG and video-EEG recordings showed that seizures started with bilateral, symmetrical flattening of the EEG for 5 to 19 sec; simultaneously there was apnea and tonic motor activity [58–61]. The EEG flattening was followed by a long (1–2 min) bilateral discharge of spikes and sharp waves; simultaneously, there were vocalizations, chewing, and focal or generalized clonic activity. The prominence of EEG and motor abnormalities varied between the left and the right from one seizure to the next in any given child. The seizures stopped without EEG or clinical postictal depression. Interictal EEG is of little assistance in making the diagnosis of BNFS. It may or may not be abnormal interictally, and no diagnostic features have been described. The abnormalities reported included spikes, sharp waves, “epileptiform” patterns, “generalized periodicity”, and slowing, but abnormal findings are mostly transient [58–61].

In many published case reports, EEG was not performed or the results were not described in sufficient detail. This the only autosomal dominant epilepsy syndrome where the molecular basis has essentially been defined, the vast majority of families carrying mutations or deletions of the potassium channel subunit genes KCNQ2 or KCNQ3 on chromosomes twenty and eight respectively [62,63].

MPSI is a newly recognized epileptic syndrome, labeled as “syndrome in development” in the ILAE diagnostic scheme [55]. It is characterized by the onset in the first 6 months of age of nearly continuous multifocal partial seizures arising independently and sequentially from both hemispheres, progression through a period of intractable seizures, subsequent neurological deterioration or arrest with complete loss of both cognitive and motor abilities, and decline of head circumference percentile [56,64–66,68–70]. To date, no etiology has been found for this disorder. Conventional AEDs have proven ineffective as well as trials with various vitamins and ketogenic diet. Successful control of seizures has been reported with potassium bromide and levetiracetam [65–67]. Approximately 50 cases of this unusual but easily overlooked epilepsy syndrome have been studied. Although the usual time of seizure onset is at 1 to 6 months, onset in the first days of life has been reported, and approximately one-half of cases had onset in the first month of life. Neuroimaging is reported as normal at onset and, when abnormal, show progressive atrophy on follow-up. At onset, interictal EEG background varies from normal to diffuse slowing [56,64,68] and epileptiform discharges may be rare,
Fig. 6. Ictal recording of an infant with migrating partial seizures in infancy. (A) A seizure starts over the left frontal region; (B) Another seizure starts over the right frontal region before the end of the first event; (C) Simultaneous ictal discharges involve two different area of the brain, the left frontal region and the right frontal region; (D) The first event ends while the second over the right frontal region persists; (E) Another ictal discharge arises from the left frontocentral region.

with a unifocal or multifocal interictal patterns. The multifocal character of the seizures may become evident only with prolonged video-EEG monitoring, suggesting that long-term monitoring plays an important role in the diagnosis of this disease [70]. EEGs reflect the escalation of seizure activity as no infant continues
to have a normal EEG. The location of the ictal onset varies not only from side to side but also within a hemisphere. Electrographically, the single ictal event can shift from one region to another and from one hemisphere to the other and additional seizures beginning in other areas in either hemisphere could start before the end of the first event, or immediately follow it [56, 64–70] (Fig. 6). The clinical semiology of seizures begins with focal motor movements that can alternate from one side of the body to another with lateral deviation of
the head and eyes and eye jerks, twitching of the eye-
lids, limb myoclonic jerks, and increased tone of one
or both limbs. In addition, it is worth mentioning that
in very young patients motor and autonomic signs are
often the only clinically relevant symptoms of seizures.
Focal motor components are often accompanied by au-
tonomic signs including flushing of the face, salivation
and apnea. Truly generalized tonic-clonic seizures are
very rare. Prolonged observation soon shows that both
sides are alternatively affected, which demonstrates the
involvement of the whole brain cortex. In a few cas-
es [56,65–67,69] seizures were eventually controlled
and these children partly recovered motor and cognitive
abilities. In all series, developmental outcome appears
better in those with better seizure control, compared
with those with continued intractable seizures. Some
patients die [56,66,67,70]. More recently, Marsh et
al. [69] published a series of infants with MPSI and a
slightly better outcome than previously reported. Given
the unique clinical and EEG features exhibited by chil-
dren with MPSI, it is extremely unlikely that this condi-
tion could be mistaken for one of the severe epileptic
syndromes of neonatal period, such EME and OS, as the
above entities do have a typical interictal EEG pattern,
such as burst-suppression in EME and OS. Differently
from OS, spasms are lacking in MPSI [56,64–70].

OS and EME represent the earliest forms of epileptic
encephalopathy. The concept of epileptic encephalopa-
thy has recently introduced and indicated a condi-
tion in which the epileptiform abnormalities themselves
are believed to contribute to the progressive disturbance
in cerebral function [55].

OS and EME are both characterized by a very ear-
ly onset, mainly within 1 month and often within the
first 10 days, and by a suppression-bursts pattern on
EEG [71,72]. For those reasons, they are also known
as neonatal epileptic encephalopathy with suppression-
burst pattern [36].

EME is characterized clinically by the onset of frag-
mentary myoclonus appearing in the first month of life,
often associated with erratic focal seizures [73,74]. On-
set sometimes occurs as early as a few hours after birth,
and postnatal movements are sometimes reported by
the mother to be of the same type as those felt at the
end of pregnancy. Erratic myoclonias shift typically
from one part of the body to another in a random and
asynchronous fashion. They are often restricted in a
finger, a toe, the eyebrows, eyelids, or lips, occurring in
the same muscle group and often migrating elsewhere
(Fig. 7). The polygraphic EEG recording demonstrates
the presence of myoclonias that are brief, single or
repetitive, and can be very frequent or nearly continu-
ous. Massive, usually bisynchronous, axial myoclonic
jerks may start from the onset of the disease or occur
later, often interspersed with erratic myoclonias [75].
Simple focal seizures are usually subtle with eye devi-
Fig. 7. Poligraphic electroencephalography recording in a 7-day-old full term infant with early myoclonic encephalopathy showing a bursts-suppression pattern. The bursts last 2–3 sec and appear synchronously and asynchronously on the two hemispheres. The polygraphic recording show an altered respiratory pattern with chest movements occurring almost exclusively during the bursts phase. The electromyography allows to demonstrate fragmentary low amplitude myoclonic jerks involving both extremities and shifting randomly from one side to another.

Flushing of the face or apnea, but they can be focal clonic involving any part of the body. Epileptic spasms are rare and generally appear late in the course of the disease, usually at around 3–4 months of age. Neurological abnormalities are constant: very severe delay in psychomotor acquisitions, marked hypotonia, and disturbed alertness, sometimes with a vegetative state. Signs of peripheral neuropathy may also occur in rare cases. Although the etiology is mostly unknown, nonketotic hyperglycinemia, pyridoxine or pyridoxal-phosphate deficiency or dependent, and congenital deficiency of the mitochondrial glutamate transporter are known to produce a similar clinical picture [75,76]. There is a high risk of familial recurrence since in most cases the disease appears to be inherited as an autosomal recessive trait. There is no effective treatment. The prognosis is poor: children with the condition survive in a persistent vegetative state or die within the first or second year of life. OS shares with EME the age at onset, the suppression-bursts EEG, and, often, the poor prognosis [36].

The main differences are the seizure types, myoclonic in EME and tonic spasms in OS. Therefore, in order to distinguish these disorders, in addition to the usual recording, it is extremely useful to record the deltoid EMG to detect massive myoclonus or tonic
spasms, and distal EMG (fingers, face) to detect erratic myoclonus. The distinction has a great importance both from a diagnostic point of view, as the search of etiology can be best directed, and from a therapeutic point of view since vigabatrin might improve OS but not EME [71,72]. Epileptic tonic spasms, the main seizure type in OS, may occur in cluster or singly, both in the awake or the sleep state. In addition, partial motor seizures are observed in more than half of the cases. Brain imaging discloses gross structural abnormalities in most cases, such as Aicardi syndrome, hemimegalencephaly, dento-olivary dysplasia, focal cortical dysplasia. However, recently a de novo mutation in the gene encoding STXBP1 has been found in individuals with OS [77]. STXBP1 is involved in synaptic vesicles release, suggesting that the functionally impaired STXBP1 may affect synaptic functions in the human brain. Psychomotor development is virtually absent or markedly retarded. Neurological examination shows variable signs, depending on the brain malformation, and is frequently asymmetrical. Some patients may show an improvement after resection of the cortical dysgenesis [78].

7. Effect of drugs on neonatal EEG

Although there are few studies documenting the effect of drugs on the neonatal EEG, it is evident that, as with older children, drugs, especially if in the toxic range, can alter background activity. Prolonged periods of inactivity on the EEG recording usually occur following a loading dose of phenobarbital and may last longer than one hr following administration. Staudt et al. [79] argued that infants with phenobarbital plasma levels above 6 mg/dL show significant background suppression. Other authors also reported the appearance of isoelectric or invariant discontinuous record after treatment with phenobarbital [11,80]. Levels greater that 25 µg/mL in neonates were reported to suppress EEG activity [71]. In their study, Ashwal and Schneider [80] found discordance between EEG activity and radionuclide uptake in infants with phenobarbital level between 25 and 35 µg/mL. The lack of EEG activity with presence of cerebral blood flow suggested that phenobarbital suppressed EEG activity. In the same study, one infant who met the clinical criteria for brain death had absent cerebral activity with level of 30 µg/mL. However, he developed some cerebral activity when the phenobarbital level fell to zero [80]. These are important observations that should be taken in account by electroencephalographers, as phenobarbital therapy is frequently administered to the neonate on a clinical basis, prior to the first EEG recording. However, this correlation was not confirmed in preterm infants. Benda et al. [19] in studying 46 preterm infants found that a mean serum level of phenobarbital of 34.5 µg/mL with a range 14–64 µg/mL did not prolonged interburst intervals during trace discontinue in preterm infants. Among medication other than AEDs that may also affect the EEG tracing, morphine has been found to produce profound, largely reversible alteration of neonatal EEG as recorded in preterm as well as full-term infants [81]. Conversely, when Bye et al. [82] investigated the effect of morphine and midazolam on background EEG of a group of neonates undergoing extracorporeal membrane oxygenation, they noted that despite midazolam and morphine serum levels were sufficient to produce adequate sedation, no patients had burst-suppressed or inactive EEG backgrounds. In addition, these authors pointed out that prolonged immobility due to sedation may lead to scalp edema and subsequent artifactual attenuation of EEG background [82].

8. Conclusions

Despite being one of the oldest tests available, EEG remains the only neurodiagnostic procedure that provides a continuous record of cerebral function over long periods. Although other advanced methods of anatomic or functional investigations provide detailed snapshots into cerebral pathophysiology, EEG provides a valuable assessment of cerebral functioning, and its evolution and structure in time. However, after having been in routine use for about half a century, EEG is currently facing unprecedented challenges in the newborn because of the survival of high-risk infants and the development of neuroprotective strategies. Therefore, its use should be extended to those centers that do not currently have access to either the equipment or expertise required for prompt neonatal EEG recording and interpretation. Interictal EEG findings are particularly useful in predicting neurologic outcome in neonates with seizures. Background EEG activity is an excellent indicator of outcome. The combination of age at onset, seizure types, interictal and ictal EEG patterns, defines an epilepsy syndrome. Delineating epilepsy syndromes in the newborn allows a greater precision in diagnosis, prognosis and treatment than simply classifying the seizure types.
References


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Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia

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ABSTRACT

Background: Therapeutic hypothermia (TH) is becoming standard of care in newborns with hypoxic-ischemic encephalopathy (HIE). The prognostic value of the EEG and the incidence of seizures during TH are uncertain.

Objective: To describe evolution of EEG background and incidence of seizures during TH, and to identify EEG patterns predictive for MRI brain injury.

Methods: A total of 41 newborns with HIE underwent TH. Continuous video-EEG was performed during hypothermia and rewarming. EEG background and seizures were reported in a standardized manner. Newborns underwent MRI after rewarming. Sensitivity and specificity of EEG background for moderate to severe MRI brain injury was assessed at 6-hour intervals during TH and rewarming.

Results: EEG background improved in 49%, remained the same in 38%, and worsened in 13%. A normal EEG had a specificity of 100% upon initiation of monitoring and 93% at later time points. Burst suppression and extremely low voltage patterns held the greatest prognostic value only after 24 hours of monitoring, with a specificity of 81% at the beginning of cooling and 100% at later time points. A discontinuous pattern was not associated with adverse outcome in most patients (73%). Electrographic seizures occurred in 34% (14/41), and 10% (4/41) developed status epilepticus. Seizures had a clinical correlate in 57% (8/14) and were subclinical in 43% (6/14).

Conclusions: Continuous video-EEG monitoring in newborns with HIE undergoing TH provides prognostic information about early MRI outcome and accurately identifies electrographic seizures, nearly half of which are subclinical. Neurology® 2011;76:556-562

GLOSSARY

AED = antiepileptic drug; BS = burst suppression; HIE = hypoxic-ischemic encephalopathy; ROC = receiver operating characteristic; SE = status epilepticus; TH = therapeutic hypothermia; UCSF = University of California, San Francisco.

Hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia is an important cause of mortality and neurologic morbidity.1-2 Randomized clinical trials have demonstrated that moderate hypothermia is associated with a reduction in death and neurologic impairment at 18 to 22 months of age.3,4 As a result, many centers now offer therapeutic hypothermia (TH) as a neuroprotective strategy for neonatal HIE.

Reliable early predictors of neurologic outcome in newborns after acute hypoxic-ischemic insult are important for counseling families and for making thoughtful treatment decisions. Clinical assessment can help with prognosis,5-7 although sedating medications and clinical changes with TH8 are complicating factors. Brain MRI is highly predictive of neurologic outcome,9,10 including in the setting of hypothermia,11 although it does not provide functional

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assessment and its sensitivity for hypoxic-ischemic injury in the first 48 hours of life is limited. A single EEG recording during the first week of life in noncooled infants with HIE, and in infants with HIE treated with TH, may help predict neurologic outcome. However, continuous video-EEG monitoring is the gold standard for evaluating brain function and for recording electrographic seizures in neonates with HIE and it has not yet been reported in neonates with HIE undergoing TH.

Our aim was to describe the evolution of the EEG background during TH and rewarming and to determine the incidence of electrographic seizures in newborns with HIE treated with moderate hypothermia. We also sought to determine the prognostic value of EEG background during TH using brain MRI as an early outcome measure.

METHODS

Consecutive newborns with HIE who underwent TH with whole-body cooling at University of California, San Francisco (UCSF), between November 2007 and July 2009 were included in this cohort study. Our TH clinical protocol is based on published trials. Selection for TH included 1) ≥36 weeks gestational age at birth, 2) any of the following: cord or first gas base deficit <5, cord or first gas pH <7.0, cord or first gas base deficit >12, 10-minute Apgar score <5, or prolonged resuscitation, and 3) moderate to severe encephalopathy within 6 hours of birth. Exclusion criteria included suspected or known congenital malformation and inborn errors of metabolism. TH was initiated as soon as possible after birth at UCSF or at the time of referral from the outside hospital and consisted of whole-body moderate hypothermia (Cincinnati Sub-Zero Blanketrol III) (target temperature 33.5°C) for 72 hours followed by rewarming over approximately 6 hours. All patients received morphine infusion throughout TH to prevent discomfort and shivering (10–25 μg/kg/h, with boluses as needed). Clinical and electrographic seizures were treated with antiepileptic drugs (AEDs) including lorazepam, phenobarbital, fosphenytoin, and levetiracetam according to institutional guidelines. Clinical data were extracted from medical records.

Standard protocol approvals, registrations, and patient consents. The Committee on Human Research at UCSF approved the retrospective review of the clinical, EEG, and imaging data for this study.

Video-EEG monitoring. Video-EEG was initiated as soon as possible after admission to the nursery. As part of our clinical protocol, infants are continuously monitored with a NicoletOne video-EEG system throughout TH and rewarming. A trained technician applied surface electrodes according to the international 10–20 system, modified for neonates. EEG recordings were interpreted by a pediatric neurophysiologist (J.S.) for clinical use in the acute setting. Using stored files, full video-EEG recordings were scored in a standardized fashion by a pediatric neurophysiologist (M.R.C.) blinded to all clinical factors except patient age. Predominant background pattern and occurrence of electrographic seizures and status epilepticus (SE), with or without clinical manifestations, were reported in 6-hour intervals with the initiation of recording as time “0.” Clinical seizures without EEG correlates were not considered. For the analysis, we used the initial 6-hour interval (beginning of cooling), the 24- to 30-hour interval (midcooling), the last interval prior to rewarming (end of cooling), and the first interval after rewarming (postcooling). A seizure was defined as a repetitive, evolving, and stereotyped pattern, with a definite beginning and end, a minimum duration of 10 seconds, and a minimal amplitude of 2 μV. SE was defined as continuous seizure activity for at least 30 minutes or recurrent seizures for over 50% of 1–3 hours of recording time. EEG background was classified into 5 patterns as previously described: 1) normal pattern for gestational age, including recordings with transient periods of discontinuous activity occupying less than 50% of the recording, with presence of distinct state changes; 2) excessively discontinuous, with persistence of discontinuous activity occupying more than 50% of the recording and consisting of bursts of normal activity separated by abnormally long, interburst intervals of more than 6 seconds duration, and amplitude <25 and >5 μV, with poor state changes; 3) depressed and undifferentiated, with persistently low-voltage background activity with amplitude between 5 and 15 μV and without normal features; 4) burst suppression (BS), invariant and unreactive pattern of bursts of paroxysmal activity with mixed features but no age-appropriate activity lasting less than 10 seconds alternating with periods of marked voltage attenuation with amplitude ≤5 μV; 5) extremely low voltage, invariant and unreactive pattern, with amplitude <5 μV or with no discernible cerebral activity.

Brain MRI. Infants were imaged shortly after rewarming (median of 5 days of life) using a specialized neonatal head coil on a 1.5-Tesla Signa EchoSpeed system (GE Medical Systems). Imaging sequences included T1- and T2-weighted MRI and diffusion-weighted imaging. A pediatric neuroradiologist (A.J.B.), blinded to the clinical history, evaluated all images. Injury was scored using a system strongly predictive of neurodevelopmental outcome following neonatal HIE. We defined normal to mild MRI injury as basal ganglia/thalamus score <2 and watershed score <3 and moderate to severe MRI injury as basal ganglia/thalamus score ≥2 (involving both the thalamus and the lentiform nucleus) or watershed pattern ≥3 (involving both watershed cortex and white matter). A similar classification was highly predictive for neurologic disability at 18 months of age in newborns with HIE treated with hypothermia.

Statistical analysis. All analyses were performed with STATA software (Stata 10.1, Stata Corporation, College Station, TX). χ² and Fisher exact tests were used to compare dichotomous variables, and t test was used for continuous variables. Wilcoxon rank sum test (Mann-Whitney U) was used to compare nonparametric data. Receiver operating characteristic (ROC) curves were used to assess the prognostic value of EEG background patterns at each time interval. We considered significant a p value <0.05.

RESULTS

Patient population. During the study period, 49 newborns were treated with hypothermia and 46 had continuous video-EEG available for review. Of these, 41 were evaluated with MRI. Five infants who were deceased following redirection of care and were not studied with MRI were excluded. Four of them had an initial extremely low voltage
cerebral activity, and one had BS pattern, both persisting for more than 24 hours. Their clinical severity was similar to those with persistent BS or extremely low voltage activity and moderate to severe MRI injury. Clinical characteristics of newborns with respect to brain injury are presented in table 1. Mean hour of life to reach target temperature was 5.2 ± 1.9.

**Video-EEG monitoring.** EEG monitoring was initiated at a mean of 10.2 ± 2.9 hours of life. All infants reached target temperature before or within 1 hour after EEG initiation. Mean duration of monitoring was 90.9 ± 28.2 hours. Nine infants received AEDs prior to the onset of EEG monitoring, and one of them subsequently developed subclinical seizures. In 2 newborns, monitoring was discontinued prior to rewarming.

**EEG background pattern.** From the beginning of cooling to rewarming, the background improved in 19 newborns (49%), remained the same in 15 (38%), and worsened in 5 (13%). EEG background pattern and the burden of moderate to severe MRI injury at each time interval are presented in table 2. The background pattern for newborns with moderate to severe injury was significantly worse than for those with no or mild injury for all monitoring time points (table 3). The sensitivity and specificity of EEG background at specified time intervals was greatest at midcooling and beyond (table 4).

**Beginning of cooling.** None of the newborns with a normal background at the beginning of cooling had moderate to severe injury. Of the 15 newborns with an excessively discontinuous pattern, 4 (27%) had moderate to severe injury, 5 had mild injury, and 6 were normal. In contrast, of the 14 newborns with BS or extremely low voltage patterns, 9 (64%) had moderate to severe injury. Of these, 4 had maximal MRI injury scores. Interestingly, 5 newborns with BS or extremely low voltage patterns at the beginning of cooling had a normal MRI or only mild injury. In all 5 cases, however, the EEG improved by 12–18 hours of recording, and in 3 of them the background normalized by midcooling.

**Midcooling.** One newborn whose EEG had normalized by this interval from a discontinuous background at the beginning of cooling had moderate to severe injury; none of the remaining 14 newborns with a normal EEG during midcooling had moderate to severe injury. Of the 13 infants with a discontinuous EEG, again about one-quarter (23%) had moderate to severe injury, accounting for 2 infants whose background was unchanged from the beginning of cooling and an additional infant whose initial background was depressed and undifferentiated. By this time period, all newborns (7/7, 100%) with BS or extremely low voltage patterns had moderate to severe injury, with 3 having maximal MRI injury scores.

**End of cooling.** Moderate to severe MRI injury was present in 1 of the 12 infants (8%) whose background was normal and 3 of the 16 infants (19%) whose background was excessively discontinuous, compared with all 5 (100%) whose background showed BS or extremely low voltage.

**Postcooling.** During this interval, the same newborn with a normal background (6%) and the same 3 newborns with a discontinuous background (27%) had moderate to severe injury. All 6 infants with BS

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**Table 1** Clinical characteristics and MRI outcome

<table>
<thead>
<tr>
<th></th>
<th>Moderate to severe MRI injury (n = 15)</th>
<th>No or mild MRI injury (n = 26)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, wk, mean ± SD</td>
<td>39.4 ± 1.5</td>
<td>39.1 ± 1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex ratio, M:F</td>
<td>1.1</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Birth weight, g, mean ± SD</td>
<td>3,234 ± 552</td>
<td>3,381 ± 760</td>
<td>0.5</td>
</tr>
<tr>
<td>10-min Apgar, median (range)</td>
<td>4 (0–7)</td>
<td>5 (1–8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cord or blood gas pH, mean ± SD</td>
<td>6.86 ± 0.19</td>
<td>6.98 ± 0.21</td>
<td>0.08</td>
</tr>
<tr>
<td>Inborn neonates, n (%)</td>
<td>0 (0)</td>
<td>4 (15)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Table 2** Evolution of EEG background with hypothermia by severity of MRI injury*

<table>
<thead>
<tr>
<th>EEG background</th>
<th>Phase of therapeutic hypothermia</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning (n = 26)</td>
<td>Mid (n = 26)</td>
<td>End (n = 26)</td>
<td>Post (n = 12)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>None/mild injury</td>
<td>Moderate/severe injury</td>
<td>None/mild injury</td>
<td>Moderate/severe injury</td>
<td>None/mild injury</td>
</tr>
<tr>
<td></td>
<td>8 (100)</td>
<td>0</td>
<td>14 (93)</td>
<td>1 (7)</td>
<td>11 (92)</td>
</tr>
<tr>
<td></td>
<td>11 (73)</td>
<td>10 (77)</td>
<td>13 (81)</td>
<td>8 (73)</td>
<td>15 (94)</td>
</tr>
<tr>
<td></td>
<td>2 (50)</td>
<td>2 (40)</td>
<td>2 (29)</td>
<td>2 (33)</td>
<td>2 (67)</td>
</tr>
<tr>
<td></td>
<td>Burst suppression</td>
<td>2 (29)</td>
<td>4 (100)</td>
<td>2 (100)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Extremely low voltage</td>
<td>3 (43)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Values are n (%).
or extremely low voltage patterns after rewarming had moderate to severe injury.

Electrographic seizures and SE. Electrographic seizures were identified in 14 newborns (34%), 4 of whom had SE. Among the 14 newborns with seizures, 13 (93%) had seizure onset within the first 18 hours of recording, 8 in the first 6 hours. One infant had seizure onset during rewarming. Recurrent seizures were recorded during midcooling in 2 patients and during rewarming in 3. Six of 14 patients (43%) never showed a clinical correlate during seizures, including 3 with subclinical SE. All 4 infants with SE had BS or extremely low voltage backgrounds at the beginning of cooling and never recovered better than depressed and undifferentiated at last time point. Isolated or recurrent seizures were more frequent in patients with moderate to severe MRI injury compared with those with no or mild injury (53% vs 23%, \( p = 0.05 \)), and SE was only seen in newborns with moderate to severe injury (\( p = 0.01 \)).

Nonsurviving infants. Among the 5 nonsurviving infants, 4 had persistent BS or extremely low voltage backgrounds throughout the duration of monitoring and maximal MRI injury, and goals of care were redirected to comfort measures. One infant had an excessively discontinuous background at the initiation of monitoring, depressed and undifferentiated by midcooling, with less severe MRI injury. Goals of care were redirected due to persistent multisystem failure.

**DISCUSSION** This study demonstrates that continuous video-EEG recording is an important diagnostic and prognostic tool in newborns with HIE undergoing TH. In our cohort, EEG background was associated with early MRI findings throughout the treatment period. A normal EEG was associated with no or mild MRI brain injury at all time points, although a normal background at the beginning of cooling was even more predictive of a favorable MRI outcome (100% specific) than at later time points (93% specific), as the EEG background of one newborn with moderate to severe MRI injury improved from excessively discontinuous to normal over the first 24 hours of monitoring. In contrast, the prognostic value of a BS pattern or extremely low voltage background for moderate to severe injury increased from the beginning of cooling (81% specific) to midcooling and thereafter (100% specific), reflecting 5 newborns with these concerning patterns at the onset of monitoring who rapidly improved by midcooling and were spared from moderate to severe MRI injury. The greatest prognostic value of EEG background in this population for predicting moderate to severe MRI brain injury was not achieved until midcooling, highlighting the importance of continuous monitoring or sequential EEGs in this population.

Our findings are substantiated by prior studies in noncooled infants with HIE, which demonstrated that a normal EEG within the first 2–7 days of life is...

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<table>
<thead>
<tr>
<th>EEG background pattern, median (range)</th>
<th>Moderate to severe MRI injury (( n = 15 ))</th>
<th>No or mild MRI injury (( n = 26 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginning of cooling</td>
<td>4 (2–5)</td>
<td>2 (1–5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Midcooling</td>
<td>3.5 (1–5)</td>
<td>1 (1–3)</td>
<td>0.0000</td>
</tr>
<tr>
<td>End of cooling</td>
<td>3 (1–5)</td>
<td>2 (1–3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Postcooling</td>
<td>3 (1–5)</td>
<td>1 (1–3)</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

**Table 3 EEG background evolution, seizures and status epilepticus, and MRI outcome**

<table>
<thead>
<tr>
<th></th>
<th>Moderate to severe MRI injury (( n = 15 ))</th>
<th>No or mild MRI injury (( n = 26 ))</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures, n (%)</td>
<td>8 (53)</td>
<td>6 (23)</td>
<td>0.05</td>
</tr>
<tr>
<td>Status epilepticus, n (%)</td>
<td>4 (27)</td>
<td>0 (0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table 4 Sensitivity and specificity of EEG background during hypothermia for moderate to severe MRI injury**

<table>
<thead>
<tr>
<th>EEG background cutpoint*</th>
<th>Phase of therapeutic hypothermia</th>
<th>Sensitivity, %b</th>
<th>Specificity, %c</th>
<th>Sensitivity, %b</th>
<th>Specificity, %c</th>
<th>Sensitivity, %b</th>
<th>Specificity, %c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning</td>
<td>100</td>
<td>31</td>
<td>93</td>
<td>54</td>
<td>93</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Mid</td>
<td>73</td>
<td>73</td>
<td>71</td>
<td>92</td>
<td>71</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>End</td>
<td>60</td>
<td>81</td>
<td>50</td>
<td>100</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>27</td>
<td>88</td>
<td>21</td>
<td>100</td>
<td>21</td>
<td>100</td>
</tr>
</tbody>
</table>

* EEG background scoring: 1 – normal; 2 – excessively discontinuous; 3 – depressed and undifferentiated; 4 – burst suppression; 5 – extremely low voltage.

b Sensitivity: Given moderate to severe injury, % identified as positive by EEG.

c Specificity: Given no moderate to severe injury, % identified as negative by EEG.

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associated with favorable developmental outcome and a severely abnormal EEG (BS or extremely low voltage) on the second day of life or thereafter is associated with poor outcome.\textsuperscript{12,14,24} The few studies that reported EEG background in this population within the first 24 hours of life\textsuperscript{17,25,26} showed a relatively poor specificity for adverse developmental outcome following a severely abnormal background during the first 12 hours of life because of EEG normalization by 12 to 24 hours of life in some infants with normal outcome. Similarly, in our cohort, a BS or extremely low voltage EEG was not highly predictive for moderate to severe MRI injury until the second day of life, around the time of midcooling. This finding is supported by a prior study evaluating EEG during hypothermia in neonatal HIE by a single sample recorded sometimes in the first 48 hours of life, which found that a background of <5 $\mu$V was associated with death or major neurologic disability.\textsuperscript{15} Similarly, a recent study evaluating the prognostic value of amplitude-integrated EEG in newborns with HIE exposed to normothermia compared to those treated with TH showed that a severely abnormal background pattern in the hypothermia-treated group was not specific for abnormal developmental outcome until 48 hours of life.\textsuperscript{27}

Our findings differ from prior studies of noncooled newborns with HIE in 2 main ways. First, prior studies have shown that a discontinuous EEG in the first several days of life is often associated with poor outcome,\textsuperscript{28-31} whereas the majority of newborns in our cohort (73%) had an excessively discontinuous pattern after rewarming had no or only mild MRI injury. While it is difficult to directly compare our study to prior studies given the differences in methodology and the wide range of definitions of discontinuous background in the literature, the outcome of newborns with an excessively discontinuous background appears to be different in newborns treated with hypothermia. Interestingly, clinical encephalopathy on the fourth day of life following TH has also been shown to be less predictive of outcome in cooled infants compared to noncooled infants.\textsuperscript{8}

Second, in comparison to the single study of continuous EEG monitoring in noncooled newborns with HIE which showed improvement of the background pattern over the first 3 days of life in all newborns,\textsuperscript{17} the background worsened over the course of monitoring in 13% of newborns in our cohort. Whether the EEG differences seen in our cohort of infants with HIE and cooling are attributed to hypothermia itself or the evolution of injury in this population is uncertain.

Electrographic seizures were present in 34% of newborns during TH, and continuous video-EEG revealed that almost 50% of newborns with seizures, including 3 with SE, had seizures without clinical correlate. Although experimental studies showed a potent effect of hypothermia in controlling seizures,\textsuperscript{32,33} a high incidence of seizures has been reported in children during TH.\textsuperscript{34} This discrepancy may be related to the earlier and deeper cooling used in animal models.\textsuperscript{32,33} Most studies rely on clinical evaluation for seizure diagnosis and classification of seizure severity in newborns.\textsuperscript{35,36} However, it is known that the majority of seizures, especially in critically ill infants, do not have a clinical correlate and will not be recognized without continuous EEG.\textsuperscript{16,57,58} Moreover, it is often impossible to accurately differentiate between seizure-related and nonseizure movements in infants using clinical evaluation alone.\textsuperscript{19} While isolated or recurrent seizures were recorded in more than 50% of infants with moderate to severe brain injury, not all were associated with moderate to severe brain injury. In contrast, all newborns with SE had severely abnormal MRI. These results are in keeping with a recent work suggesting that a significantly worse outcome occurs in newborns with SE compared to newborns with recurrent seizures.\textsuperscript{20}

There are several limitations to our study. First, due to the referral pattern at our institution, newborns did not start monitoring at the exact same time in the first day of life. However, in most of our patients, monitoring was initiated within the first 12 hours of life. Second, an excessively discontinuous background by our system encompassed a broad range of interburst intervals. Therefore, it is not surprising that a discontinuous pattern was a relatively poor predictor of MRI brain injury. Third, we used MRI as a short-term outcome measure and do not yet know the long-term outcome in this cohort. It has been reported that hypothermia does not affect the prognostic value of MRI in newborns with HIE.\textsuperscript{11} However, long-term developmental follow-up of this cohort is needed to confirm our results. Finally, as many patients with poor EEG backgrounds and moderate to severe brain injury were treated with AEDs, we were unable to assess whether depressed background activity was an effect of medication or due to underlying brain injury.

EEG monitoring in newborns is noninvasive, provides data from the entire cortex, and can be easily performed at the bedside. Our findings underscore the importance of continuous EEG monitoring in this population to assist with seizure management and discussions regarding prognosis and goals of care. Even in the setting of hypothermia, EEG remains a strong predictive tool, and its routine use alongside clinical evaluation and MRI is warranted.
Establishing consensus on neonatal EEG nomenclature and classification will help future studies on the prognostic value of EEG during TH. Particularly, further analysis and revalidation of the excessively discontinuous pattern in neonates being treated with HIE is warranted. Given emerging data suggesting that seizures may be associated with increased brain injury following neonatal HIE, accurate seizure detection is becoming an important issue in the context of neuroprotection. Future studies that evaluate whether rapid and effective treatment of seizures will improve neurologic outcome will rely on continuous EEG monitoring.

AUTHOR CONTRIBUTIONS
Statistical analysis was conducted by Dr. H.C. Glass, Dr. S.L. Bonifacio, and Dr. K.B. Nash.

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