Review Article

The role of electroencephalography in neonatal seizures

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S eizures are the most frequent, and often the only clinical sign of central nervous system dysfunction in neonates.[1] Seizures usually reflect an insult to the central nervous system and, their recognition is important because they are associated with a high morbidity and mortality rate.[2] Three seizure types have been described in neonates: clinical, subclinical/electrographic, and electroclinical. Mizrahi and Kellaway[1] using video-EEG in infants have shown that a significant number of abnormal movements previously thought to be seizures do not have simultaneous ictal EEG discharges (clinical only). EEG seizures without clinical manifestations (subclinical or electrographic) have been well described in infants.[1,2] Over 70% of seizures in a group of 41 'high risk' neonates were electrographic only, the remainder were electroclinical, consisting of simultaneous electrographic and clinical seizures.[3,4]

The incidence of seizures in infants born at term is 1.5-3 per 1000 live births, the incidence is even higher in preterm infants, ranging from 50-150 per 1000 live births.[5] These figures are probably under-estimations as these figures only include clinical and electroclinical seizures. The exact incidence of electrographic, clinically silent seizures is unknown.[6] Continuous monitoring of infants after one clinical seizure showed that 79% of subsequent EEG seizures were clinically silent.[3] Such phenomena seems to be more common in preterm infants.[7]

A recent study has shown that seizures in the newborn are often clinically silent (electrographic), and that the extent of the electrographic seizure burden in sick baby is often greatly underestimated.[8] Electrographic seizures cannot be diagnosed without EEG. Video-EEG has been shown to be the most useful technique available to identify, classify, and quantify neonatal seizures.[8]

In Indonesia especially in neonatal intensive care units, the use of EEG is not well-known due to lack of knowledge and unavailability of the equipment. This paper gives an overview of the important role of EEG in detection, classification, management and prognosis of neonatal seizures.

Neonatal electroencephalography

Neonatal EEG is one of objective methods for measuring the functional integrity of the immature cortex and its connections. Empirically, it is most commonly used to measure the impact of a known medical or neurological insult to the brain and to detect or confirm the presence of seizures.[9] This is different with other techniques, such as ultrasonography and neuroimaging studies, that assess brain structure.[1]

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Before recording neonatal EEG the infants's medical history and clinical finding should be studied. During EEG recording the patient should be observed carefully and stimulated appropriately. EEG findings should be considered in relation with the infant's state of alertness and with the relevant laboratory data. The patient's condition should be discussed by neurophysiologist and the physician who requested EEG examination.[1]

The timing of EEG examinations may have a substantial impact on its interpretation. It is inadequate to simply record a single EEG near the end of the patient's hospital stay. Normalization may occur after the peak of an illness (the time when the EEG is most likely to reveal its maximal degree of abnormality). The EEG may show substantial improvement in parallel with clinical signs of neurological recovery. Because EEG abnormalities are most commonly obtained in the acute phase of neurological diseases, it is critical that one or more studies be obtained when the infant is most likely to display the most revealing prognostic information.[9]

The EEG can also provide information that the observed neurological phenomena are seizures. However, it was not all clinical seizures could be detected by EEG, particularly certain subtle seizures, most generalized tonic seizures and focal and multifocal myoclonic seizures.[10,11] Two explanations have been proposed. The first is that some seizures may be originated at a subcortical level (myclonic seizures) and are not propagated to surface electrodes because of the immature synaptogenesis and cortical projections.[1,12] The second and more probable is that subtle and generalized tonic seizures i.e. are not, in fact epileptic, or due to central nervous system hypersynchronous electrical discharges but they are still a primitive brain stem and spinal motor patterns released from tonic inhibition normally exerted by the forebrain.[13]

EEG definitions vary, but discharges are considered to be seizures if they last more than 5 or 10 seconds. Neonatal electroencephalographic seizures are usually not sustained. The typical duration of the electrographic neonatal seizure is 2-3 minutes, but many seizures will be shorter, particularly in preterm infants.[14] In spite of this, the total seizure burden can be very significant. Most neonatal seizures

have a focal onset, whereas a generalized onset of a spike and wave seizure discharge is extremely rare. Neonates can display simultaneously independent focal electrographic seizures. Neonatal status is currently defined as a total seizure time occupying 50% or more of the recording time. Background abnormality is correlated with the severity of the brain lesion. Abnormal background activity is associated with an increased risk of seizures and poor neurodevelopmental outcome.[15]

Discharges of less than 10 second duration is defined as BIRDs (Brief Interictal Rhythmic Discharges or Brief Ictal Rhythmic Discharges) and are of uncertain significance. However, BIRDs have been associated with seizures in the same or subsequent EEG and with poor neurodevelopmental outcome.[16]

Continuous (24 hours) EEG recording is recommended for infants who are paralysed, to detect the frequency and duration of seizures.[17] Only continuous EEG can reliably detect and measure the neonatal seizure burden because there is a poor correlation between the clinical and electrographic manifestations of seizure in the newborn.[8]

EEG monitoring is an essential part of seizure definition and recognition, making it a necessity along with clinical semiology to define the seizure type and changes in seizure frequency.[18]

Detection of neonatal seizures

Neonatal seizures can be viewed as a nonspecific response of the immature central nervous system to diverse insults. Neonatal seizures differ in clinical semiology from those in adults and seizures in preterm infants differ from those in term infants. Cerebral cortical organization, synaptogenesis, and myelination of cortical efferent pathways are poorly developed in human neonates, leading to weakly propagated, fragmentary seizures whose electrical activity may not spread to surface EEG electrodes. The more advanced development of the limbic system with connections to midbrain and brainstem may explain the higher frequency of mouthing, eye deviation, and apneu in neonates than seizures in adults. Thus the clinical manifestations can be extremely inconspicuous in neonates.[19]

Electroencephalography may be useful for confirming neonatal seizures. However not all seizures have EEG findings correlation, which makes diagnosis difficult. Mizrahi and Kellaway[1] differentiated seizures that had a consistent EEG pictures, such as focal clonic seizures, from those that had no consistent EEG patterns, such as subtle seizures.

Proper identification of epileptic seizures is important. The most common seizure types are focal or multifocal clonic, tonic, and myoclonic and subtle. Subtle seizures comprise a variety of motor and autonomic phenomena and are more common in neonates who have severe encephalopathies. However, neonates often have abnormal paroxysmal motor activity, such as oral-buccal-lingual movements, pedaling, stepping, and rotatory arm movements, that are not associated with ictal EEG patterns. These non epileptic events do not require anticonvulsant drugs. The EEG is of particular value for detecting subclinical seizures (EEG seizures without clinical manifestations) and for distinguishing subtle seizures from nonepileptic behaviours.[20]

Classification of neonatal seizures and correlation with EEG

The most widely used classification system is one initially proposed and periodically updated by Volpe. The latest revisions, although not based on EEG-video monitoring, do take into account the possibility that some seizures types may occur in the absence of simultaneous EEG seizure activity and expands the categories of clinical seizures.[1,5] (**Table 1**)

Table 1. Classification of neonatal seizures

Clinical seizure	Electrographic Seizure	
	Common	Uncommon
Subtle	+[a]	
Clonic		
Focal	+	
Multifocal	+	
Tonic		
Focal	+	
Generalized		+
Myoclonic		
Focal,multifocal		+
Generalized	+	

[a] Only specific varieties of subtle seizures are commonly associated with simultaneous EEG seizure activity.

Neonatal seizures have also been characterized and classified according to their clinical features, their response to clinical stimulation and restraint of the infant, and their relationship of the clinical events to EEG seizure activity. The clinical and electroencephalographic features, taken together, form the basis for seizure classification according to type and presumed pathophysiology. The assignment of presumed pathophysiology is based not only on the presence or absence of associated EEG seizure activity, but more important on the response of the infant to stimulation and restraint. Thus, if tactile or proprioceptive stimulation of the neonate can provoke a clinical event similar to those that occur spontaneously, or if the spontaneous or evoked clinical events can be suppressed by restraining or repositioning of the infant, the spontaneous events can be designated to be of nonepileptic origin.[1]

1. Subtle

Subtle seizures, such as bicycling movements, lip smacking, roving eye movements, and apneu, are more commonly seen in preterm infants than term infants. The most common manifestations of subtle seizures in both preterm and full term infants are ocular movements. In full-term infants, there is usually horizontal sustained deviation of the eyes. In preterm infants, the ictal manifestation is most commonly sustained eye opening, with unresponsiveess and ocular fixation. Other examples include chewing or other oral-buccal-lingual movements, pedaling motions or other stereotypic limb movements, autonomic phenomena, and apneic spells. The frequency with which these clinical seizure types are associated with concomitant EEG activity is controversial. Typically, these seizures shows no electrographic correlation. Research in infants with hypoxic-ischemic encephalopathy, video EEG monitoring has demonstrated that infants with subtle seizures can have variable cortical EEG patterns with subtle seizures, sometimes exhibiting cortical rhythmic electrographic seizure activity, and at other times, no discrete EEG correlate.[21]

2. Clonic seizures

Clonic seizures can either be focal or multifocal. These seizures are more typically seen in term infants than

those in preterm infants, and are almost invariably associated with surface EEG rhythmic electrographic seizure activity, usually trains of theta or alpha range frequencies.[2] These seizures can occur sequentially or simultaneously, often with different and distinct surface EEG findings.[21]

3. Tonic seizures

Tonic seizures represent a mixed group, some are probably secondary to brainstem injury/dysfunction, whereas others have a distinct EEG correlation with surface EEG monitoring. Generalized tonic seizures are not commonly associated with an electrographic pattern unless there are associated autonomic phenomena. If the tonic seizures contain focal features, such as unilateral involvement or eye deviation, there is usually an EEG correlated with surface EEG monitoring.[21]

4. Myoclonic seizures

Myoclonic seizures are seen in both preterm and term infants. They may or may not have an EEG correlation. If the myoclonus is related to sleep or hypoxic ischemic injury, there is usually no EEG correlation.[1,2,5] Specifically, some newborns will have exaggregated physiologic myoclonus of sleep. Infants with hypoxic-ischemic injury may suffer from anoxic myoclonus, which probably reflects brain stem injury. On the other hand, there are special syndromes in which the presence of myoclonus may signify a catastrophic epilepsy of infancy, such as Ohtahara's syndrome or early myoclonic epileptic encephalopathy. These two syndromes are associated with a burst suppression pattern on EEG and have poor prognosis.[21]

In reviewing the electroencephalography of neonates, the most common ictal EEG findings are rhythmic trains of alpha, beta, or theta waves.[2] In multifocal clonic activity, the electrographic seizures may initially start in one region of the brain at a certain rhythmic frequency, followed by a second discharge pattern, perhaps at a completely different rate and rhythmicity in a different anatomical area of the brain. This again reflects the relative immaturity of the cortical-cortical network of the newborn brain.[21]

Common epileptic syndromes

Some etiologies of neonatal seizures (epileptic syndromes, hypoxic-ischemic encephalopathy, and metabolic disorders) may show specific EEG patterns.

1. Benign idiopathic neonatal convulsions

Benign idiopathic neonatal convulsions occur around the fifth day of life (day 1 to day 7, with 90% between day 4 and 6) in otherwise healthy neonates. At present the etiology is unknown. Seizures are clonic, mostly partial and/or apnoeic.[6] The interictal EEG shows 'theta pointu alternant' in 60%, in the remaining neonates the background activity is either discontinuous, with focal or multifocal abnormalities, or normal in approximately 10%. Ictal recordings show unilateral or generalized rhythmic spikes or slow-waves mainly in the Rolandic regions though they can also be localized anywhere else. The ictal EEG paroxysm maybe unilateral, generalized or first localized and then generalized.[22] Treatment may not be necessary, but the diagnosis is one of exclusion. Seizures usually resolve by 24 hours. The outcome is good, but increased risk of minor neurological impairment has been reported.[6]

2. Benign familial neonatal convulsions

Benign familial neonatal convulsions constitute a rare disorder with autosomal dominant inheritance (mutations in the voltage-gated potassium channel genes, most cases 20q13.3, few families 8q24). Seizures occur mostly on the second or third day of life in otherwise healthy neonates and tend to persist longer than in benign idiopathic neonatal convulsions. They are mainly clonic, sometimes with apnoeic spells, tonic seizures have rarely been described.[6] Interictal EEGs can be normal, discontinuous, have focal or multifocal abnormalities or have a theta pointu alternant pattern. The ictal EEG commonly starts with a synchronous and bilateral flattening of 5-19 s coinciding with apnoea and tonic motor activity. This is followed by bilateral and often asymmetrical discharges of spikes and sharp waves with duration of 1-2 minutes, which coincide with vocalizations, chewing and focal or generalized clonic activity.[22] The background activity is normal with no specific pattern. Therapy is controversial and

probably not necessary. The outcome is favourable, but secondary epilepsy may occur in 10-15%.[6]

3. Early myoclonic encephalopathy

Early myoclonic encephalopathy is a syndrome often associated with inborn errors of metabolism, but cerebral malformations have also been reported. Onset is nearly always in the first month of life and ictal manifestations are as follows: (1) partial or fragmented myoclonus, (2) massive myoclonus, (3) partial motor seizures, (4) tonic spasms.[6] The inter-ictal EEG of early myoclonic encephalopathy is a repetitive suppression-burst pattern without physiological rhytm. The burst of high-amplitude spikes and sharp slow waves last for 1-5 s and alternate with periods of a flat or almost flat EEG lasting 3-10 s. In most cases the suppression-burst pattern becomes more apparent during deep sleep and may not occur in the EEG of wakefulness. The suppression-burst pattern may appear late at 1-5 months of age in some cases and characteristically persists for a prolonged period.[22] Seizures are resistant to treatment, though ACTH may have some temporary effect. All infants are severely neurologically abnormal and half of them die before the age of one year.[6]

4. Early infantile epileptic encephalopathy with burst-supression pattern (Ohtahara syndrome)

Age at onset is in the first three months of life with frequent tonic spasms (100-300 per day), often in clusters.[23] Partial motor seizures may also occur. The EEG suppression-burst patterns has a pseudorhythmic periodicity. The burst consists of high-amplitude slow waves intermixed with spikes lasting for 2-6 s. The suppression period of a flat or nearly flat EEG lasts for 3-5 s. The interval between the onsets of two successive bursts in the range of 5-10 s. This pattern occurs during both the waking and sleeping stages.[22] Seizures are resistant to treatment, though ACTH may have some temporary effect. The prognosis is serious with death or severe psychomotor retardation.[6]

5. Glycine encephalopathy (neonatal non-ketotic hyperglycinemia)

This inborn error of metabolism usually presents with an early myoclonic encephalopathy with seizures myoclonic elicited by tactile and painful stimuli on the second or third day of life. Associated respiratory distress syndrome, with periodic respiration, and coma are found. The EEG shows periodic discharges on a nearly silent background.[6,16]

6. Pyridoxine dependency

Pyridoxine dependent seizures are a rare but treatable, which can begin in intrauterine life. Pyridoxine is required for the synthesis of gamma amino butyric acid (GABA). In these infants, large quantities of pyridoxine are required to maintain adequate production of GABA. The diagnosis is difficult because it is one of exclusion Generalized clonic seizures usually begin shortly after birth and are resistant to conventional antiepileptic drugs (AEDs). The EEG shows burst-suppression pattern or other generalized epileptiform activity. When pyridoxine dependency is suspected, 100-200 mg of pyridoxine should be given intravenously under EEG control. The seizures will abruptly stop and the EEG will normalize during the next few hours. A subgroup of affected babies responds only to a very high dose given for two weeks.[6]

7. Seizures in hypoxic-ischemic encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is a common and important cause of seizures in term neonates. The characteristic time of onset of seizures in HIE is 8-26 hours after birth. Seizures occurring before that, are usually clinical only and are due to an abnormal increase in tone. This appears to be similar to studies in lambs in which the EEG activity with an intrapartum insult is at first depressed, and then evolves to show seizure activity about eight hours after birth.[24] An EEG obtained shortly after birth in which electrographic seizure activity is already manifest, would strongly suggest an insult over eight hours before delivery. Early background EEG activity is a relatively reliable prognostic indicator for outcome.[24,25]

Management

As soon as seizures have been detected clinically or electrographically, therapy should be started. The EEG is important to monitor the response to therapy. After

seizures have disappeared the next step is to decide when the anticonvulsant should be withdrawn.

Neonatal seizures often require continuous video EEG monitoring. Specifically, even if the clinical seizures are effectively treated, there are frequent electrographic seizures that may not be recognized.[26] Several studies indicate that clinical observation without the assistance of concomitant EEG monitoring significantly underestimates the true seizure frequency in neonates. Clancy at al studied 41 infants with neonatal seizures to determine how often their electrographic seizures were subclinical. The seizures are the result of diverse etiologies and the infants had already received one or more antiepileptic medications. Of the 393 captured seizures, only 21% (84) were observed clinically.[3] The remainder were occult, with no obvious clinical symptoms or changes in vital signs. In another study, Mac Bride et al found that neonates who had cardiac surgery almost always had intermittent electrographic seizures, none of which were clinically recognizable. They argued that video EEG monitoring should be performed routinely in this patients.[26]

The EEG may be used to monitor the effects of medication. An increase in electroclinical dissociation has been reported after treatment with phenobarbital, a reduction of electro-clinical seizures is associated with an increase of electrographic seizures and thus may give the false impression of successful treatment when no EEG is recorded.[16]

There is much debate whether or not clinical seizures without EEG correlation should be treated vigorously with antiepileptic medication. There is also debate whether electrographic neonatal seizures without clinical correlation should be treated aggressively. There are currently no well-established guidelines.[27] Studies by Toet and Hellstrom-Westass[28,29] have shown that treatment of both clinical and subclinical seizures with continuous monitoring can give a better prognosis for the newborns. The incidence of postnatal epilepsy (PNE) has decreased from 20-50% (only treating clinical seizures)[30,31] to 9.4% and 8.3%.[28,29]

In view of the animal data indicating that both electrographic and clinical seizures may have long-term detrimental behavioral and cognitive consequences on the immature brain, aggressive treatment of all seizures is important, and underscores the importance of continuous computerized video EEG monitoring.[27]

Boylan *et al*[32] stated that phenobarbitone is not effective in controlling the electrographic seizure and as more and more evidence accumulates regarding potential detrimental effects of electroclinical and electrographic seizures in neonates more effective and specific anticonvulsant medication is urgently required. The study by Boylan showed the importance of EEG monitoring as a tool to measure seizure control in the neonate. It is an effective seizure control in the neonate, therefore implies abolition of clinical and electrographic seizures.[8]

Many of the commonly used anticonvulsant regimens are ineffective in controlling seizures, clinically or electrically. Abnormal EEG activity still persists in a significant proportion of neonates who show a clinical response.[33,34] After clinical seizure control persisting EEG seizures are rarely treated, as they tend to be brief and fragmentary and further treatment increases the risk of side effects. Many of anticonvulsants cause respiratory depression and impair myocardial function.[17]

The possible adverse effects of continuing anticonvulsant treatment for several months on the developing CNS have raised concern. This prompted a Swedish study to evaluate the risk at seizure recurrence following early anticonvulsant withdrawal once seizures were controlled and subsequent EEGs did not show recurrent seizures or multiform epileptiform activity.[29] Evans and Levenne[17] recommended to withdraw anticonvulsant treatment once seizures are controlled and the neurological examination is normal. In most cases, this can be achieved prior to discharge from the neonatal unit.

Prognosis

When used as a neonatal prognostic tool, the initial recording must be made between 12 and 48 hour afterbirth, and then between 4 and 8 days of life. Severe EEG abnormalities before 12 hour of life have been reported to have no reliable prognostic value but may help in the choice of early neuroprotective treatment of acute cerebral hypoxia-ischemia.[35] In contrast Toet *et al*[36] has shown that the early (3 hours after birth) recorded amplitude integrated EEG (aEEG) has a clear prognostic significance.

Interictal background EEG abnormalities are helpful in determining prognosis in both term and preterm infants. A poor prognosis is associated with burst-supression and persistent low voltage states, although experience is required when assesing EEGs of preterm infants, as these normally show discontinuous activity with long interburst intervals.[17] Characteristics of the clinical seizures and the EEG often are useful predictors. Early onset seizures and frequent or prolonged seizures that are refractory to multiple anticonvulsants generally have a poor prognosis. In term newborn, the interictal EEG may be useful for predicting outcome. A normal interictal EEG is associated with an 85% chance of normal development compared with isoelectric, low-voltage, or paroxysmal burst-supression background activity, which generally is associated with a poor outcome.[37] Background abnormality is correlated to the severity of the brain lesion. Abnormal background activity is associated with an increase risk of seizures and poor neurodevelopmental outcome.[15] Post neonatal seizures and abnormal interictal EEG are the most important predictors of adverse outcome.[19]

The study of Menache *et al*[38] indicated that an easily measurable single EEG parameter of the excessively discontinous neonatal EEG is significantly related to to unfavourable neurologic outcome. Thus an infant whose EEG contains a predominant interburst interval duration of more than 30 seconds has a 100% probability of experiencing severe neurologic disabilities or death and an 86% chance of developing epilepsy. In critically ill infant during early neonatal period, neurologic examination may be hindered by sedation, and neuroimaging may be delayed. In these situations, decision making is difficult and quantifiable EEG parameter could be valuable for the estimation of outcome.

Mc Bride *et al*[26] found that infants with electrographic seizures correlated with microcephaly, severe cerebral palsy and failure to thrive. Zupanc[21] found that 56% infants with electrographics seizure developed epilepsy, cerebral palsy and developmental delay. Results from Boylan *et al*[32] confirmed the outlining of the predictive value of the background EEG in infants with seizures. Infants with a severe abnormal background EEG either died or had a moderate to profound disability.

However, caution must be exercised in predicting outcome based on EEG findings because of technical and interpretive difficulties with the procedure. This applies especially to preterm newborns and term infants who have mild or moderate abnormalities on EEG.[37]

In conclusion, EEG, a non-invasive cerebral investigation, is a useful tool for detection, diagnosis, evaluation of therapy and to determine the prognosis of neonatal seizures. One must keep in mind that treatment of both clinical and subclinical seizures can give a better prognosis. Interpretation of EEG in neonates is not easy and needs skills and experience. The use of EEG in the perinatology ward especially for neonatal seizures is a necessity to improve the outcome.

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