The Diagnosis and Treatment of Neonatal Seizures

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The occurrence of neonatal seizures is an important clinical sign indicating brain disorder in neonates. An identification of neonatal seizures is critical in the management of high risk neonates. However, the diagnosis and management of neonatal seizures are challenging, because electroclinical dissociation is an outstanding feature of neonatal seizures. Neonatal seizures are frequently not accompanied by any identifiable clinical symptoms even on close observation, whereas motor phenomena which have been considered to be seizures are not associated with ictal electroencephalography (EEG) correlates. For this reason, neonatal seizures should be diagnosed based on ictal EEG findings and the efficacy of treatment should be evaluated using continuous EEG monitoring. EEG is also useful diagnosing the underlying etiology of neonatal seizures. Although conventional EEG is the gold standard for the diagnosis of neonatal seizures, amplitude-integrated EEG (aEEG) can be considered an option. However, aEEG has substantial limitations. In treatment two aspects must be considered. First, neonatal seizures themselves require emergency therapy and second, etiology-specific therapy is important in order to prevent further brain injury. At present, evidence is limited on the treatment of neonatal seizures. In order to establish effective treatment, studies using continuous EEG/aEEG monitoring and long-term follow-up are necessary. Widespread use of EEG/aEEG is desirable in order to solve several problems in the diagnosis and treatment of neonatal seizures. *(Chang Gung Med J 2012;35:365-72)*

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The occurrence of neonatal seizures may be the first, and sometimes the only, clinical sign of a central nervous system disorder in neonates. Neonatal seizures may indicate the presence of a potentially treatable etiology. Thus, identification of neonatal seizures is critical in the management of high risk neonates. Most often, neonatal seizures are noted by the presence of overt motor phenomena such as convulsive movements and abnormal posturing. However, seizure manifestations are largely different from those in older children.[1-3] The motor phenomena associated with neonatal seizures are less organized and well-organized generalized tonic-clonic convulsions are not observed.[4] Moreover, recent studies using ictal conventional electroencephalography (EEG) or monitoring with amplitude-integrated EEG (aEEG) revealed that a large majority of neonatal seizures are not accompanied by any identifiable motor phenomena or other clinical symptoms, even on close observation.[5-10] In contrast,

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some motor phenomena which have been considered to be seizures by direct clinical observation are not associated with ictal EEG correlates.[11-13] These facts strongly indicate that electroclinical dissociation is an outstanding feature of neonatal seizures. For this reason, the diagnosis of neonatal seizures is a challenging issue, and must be based on conventional ictal EEG findings.[14] Conventional EEG may also give a clue to the underlying etiology. Treatment is another important issue. At present, no firm evidence has established indicationsfor treatment and the efficacy of antiepileptic drugs. This is partly attributable to inappropriate diagnosis and monitoring of neonatal seizures. EEG/aEEG is essential in evaluating the efficacy of treatment.

In this review, the importance of conventional EEG and aEEG in the diagnosis of neonatal seizures is described. Conventional EEG is the gold standard. aEEG is easy to record and interpret, and is suitable for long-term monitoring. Sufficient knowledge of these two methods is essential for optimal diagnosis and treatment of neonatal seizures.

The diagnosis of neonatal seizures and usefulness of conventional EEG

Two important aspects of neonatal seizures must be considered in order to diagnose them correctly. In most neonatal intensive care units (NICUs), neonatal seizures have generally been identified only by direct clinical observation. However, there is usually a lack of objectivity when categorizing seizures as epileptic or non-epileptic.[5,15] As mentioned above, the most important feature of neonatal seizures is electroclinical dissociation. Murray et al. compared seizures recorded on continuous video-EEG with those recognized clinically by experienced neonatal staff.[5] Of a total of 526 electrographic seizures, only 179 (34%) had clinical manifestations evident on the simultaneous video recording. In contrast, overdiagnosis occurred frequently. Electrographic evidence of seizure activity was found only in 48 (27%) of the 177 clinically suspected seizure episodes. This indicated that only 9% (48/526) of electrographic seizures were accompanied by clinical manifestations. Malone et al. investigated the accuracy and interobserver reliability of healthcare professionals in distinguishing clinically manifested seizures from other neonatal movements.[15] The average number of correctly identified events was 10/20. Of note, subtle seizures were poorly identified (range 20.4-49.6%). The interobserver agreement (κ value) for doctors and other health care professionals was poor at 0.21 and 0.29, respectively. Agreement with the correct diagnosis was also poor at 0.09 for doctors and –0.02 for other healthcare professionals. These facts strongly suggest that ictal EEG recording is essential for the accurate identification of neonatal seizures of cortical origin and distinction from non-epileptic paroxysmal events of non-cortical origin.

The second important aspect is determination of the underlying etiology of neonatal seizures. These etiologies are diverse, and include genetic epilepsies, developmental brain malformations, central nervous system infections, and fetal/neonatal asphyxia. A large majority of neonatal seizures are caused by acute symptomatic etiology such as hypoxic-ischemic encephalopathy, acute metabolic disorders, and central nervous system infections.[3,4,16,17] Fundamentally, these acute symptomatic neonatal seizures should not be classified as epilepsy, because epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.[18] Neonatal seizures of acute symptomatic etiology are usually self-limiting irrespective of treatment. Some are caused by remote symptomatic etiology such as brain malformation due to genetic origin, congenital viral infection, and intrauterine -acquired brain lesions. Remote symptomatic neonatal seizures are mostly analogous to epilepsy of neonatal onset. Rarely, neonatal seizures are of genetic origin such as benign familial neonatal seizures. In order to determine the etiology, evaluation of background EEG activities is quite useful.

The electrographic features of seizures in neonates are unique to this period.[19] Ictal EEG changes of neonatal seizures are characterized by rhythmic, repetitive, and stereotyped discharges lasting for at least 10 seconds on two or more EEG channels (Fig. 1).[20,21] Ictal EEG discharges are principally focal and restricted to relatively circumscribed regions of the brain.[22,23] All ictal EEG changes in neonates begin focally, except for the more generalized activities associated with myoclonic jerks or epileptic spasms. Ictal EEG changes may be unifocal or multifocal. Even in a single infant, ictal EEG changes can arise from different foci at different times. During a single seizure, EEG foci often migrate from one area to another within

one cerebral hemisphere or from one hemisphere to the other (Fig. 2).[19,24] The frequency, voltage and morphology of ictal EEG discharges may vary widely within a single seizure or from one seizure to the next in a given infant. Ictal EEG discharges are often in delta or theta ranges rather than alpha or beta ranges.[25] A spiky or sharp morphology of ictal EEG discharges is rather infrequent. We should suspect ictal EEG changes when we see rhythmic, repetitive, and stereotyped discharges lasting for at least 10 seconds in any morphology of EEG discharges. Evolutional changes of EEG discharges are also an important feature of ictal EEG changes. Ictal EEG discharges may begin with similar frequencies, voltage, and morphology that remain relatively constant throughout a seizure. However, ictal EEG discharges more often show evolutional changes in frequency, voltage, and morphology. These evolutional changes are an important clue to differentiate ictal EEG changes from non-epileptic rhythmic activity or artifacts. Frequency, voltage and morphology of ictal EEG discharges and their pattern of propagation are widely different among individuals even with the same etiology. On the contrary, similar patterns of ictal EEG changes can be seen in infants with neonatal seizures of different etiologies. Therefore, it is difficult to distinguish the underlying etiology of neonatal seizures on the basis of ictal EEG findings.

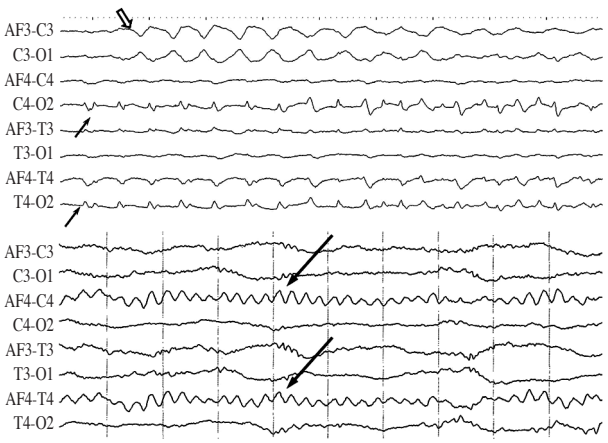

Fig. 1 Ictal EEG changes in neonatal seizures. Ictal EEG changes in neonatal seizures are characterized by rhythmic, repetitive, and stereotyped discharges lasting for at least 10 seconds on two or more EEG channels. In the upper sample, two different ictal EEG foci, in the left central (broad arrow) and right occipital (narrow arrows) areas, are observed simultaneously. In the lower sample, repetitive, rhythmic, and stereotyped δ/θ waves are observed in the right frontal area (arrows).

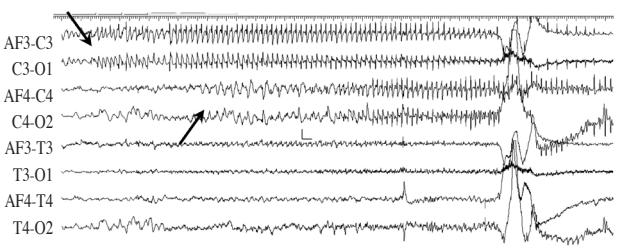

Fig. 2 A shift of ictal EEG foci during a single seizure. In this ictal EEG sample, the ictal EEG foci was first observed in the left central area (upper arrow), and then shifted to the right central areas (lower arrow) during a single seizure.

Identification of the underlying etiology is quite important in treating infants with neonatal seizures. The treatment of the underlying etiology of seizures of acute symptomatic origin is far more important than the treatment of the seizures themselves. On the other hand, vigorous treatment of the seizures themselves is necessary for neonatal seizures of remote symptomatic etiology. Catastrophic epilepsy of neonatal onset such as unilateral megalencephaly associated with early myoclonic encephalopathy with a suppression burst EEG pattern can result in severe neurologic deficit when appropriate therapy including neurosurgery is not performed. Therefore, we must be aware of the importance of identification of the underlying etiology of neonatal seizures. Evaluation of background EEG activities during the interictal period is useful in the diagnosis. Acute stage EEG abnormalities characterized by suppression of background EEG activities are often observed in infants with neonatal seizures of acute symptomatic etiology,[25-27] whereas chronic stage EEG abnormalities characterized by abnormal morphology of background EEG activities are frequently seen with remote symptomatic origins.[25,26,28-31] Background EEG activities are unremarkable in infants with benign familial or nonfamilial neonatal seizures.

Sufficient knowledge of physiological EEG findings in neonates according to their post-conceptional age (gestational age plus postnatal age) is necessary in order to evaluate background EEG activities. The key concept in understanding abnormal EEG findings in neonates is to consider not only EEG alterations in the acute stage of brain damage but also those in the chronic or recovery stage (Fig. 3). It is particularly useful to differentiate acute and

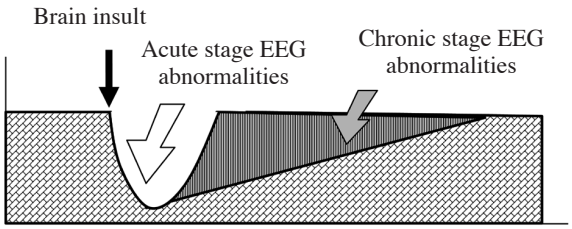

Fig. 3 Chronological EEG changes after acute brain insult. The key concept in understanding abnormal EEG findings in neonates is to consider not only EEG alterations in the acute stage of brain damage but also those in the chronic or recovery stage.

chronic stage EEG abnormalities.[25,26] We classified changes in continuity, frequency and amplitude as acute stage EEG abnormalities, and changes in maturity and wave forms as chronic stage EEG abnormalities. Abnormalities in synchrony, or sleep state usually do not occur alone and are associated with other findings.

The usefulness of amplitude-integrated EEG

It is clear that conventional EEG is quite useful for detection of neonatal seizures and diagnosis of the underlying etiology. However, the interpretation of conventional EEG is a highly specialized skill. Worldwide, there are few physicians who can interpret neonatal EEG appropriately. Since the late 1990s, aEEG has been applied in the NICU.[32]

aEEG is a simplified EEG technique suitable for monitoring the brain function of neonates.[33] At present, multichannel aEEG recordings are available using several digital devices, although the initial device was able to record only a single channel from one pair of bilaterally placed electrodes. In aEEG, the EEG signal is amplified and passed through an asymmetric band-pass filter that strongly attenuates activity less than 2 Hz and more than 15 Hz to minimize artifacts. Thereafter, signal processing is done including semilogarithmic amplitude compression, rectification, smoothing, and time compression. The signal is expressed as a semilogarithmic scale in order to enhance changes in EEG activities of very low amplitude (< 5 μV).

aEEG is also suitable for detection of neonatal seizures. As already mentioned, EEG demonstrates rhythmic, repetitive, and stereotyped discharges lasting for at least 10 seconds during neonatal seizures. Such EEG changes result in a transient rise in the aEEG amplitude, both upper and lower borders, or sometimes only the lower border (Fig. 4). Usually, neonatal seizures occur in clusters or continuously. In these cases, aEEG shows a saw-tooth pattern, that is, (semi-) periodic repetitions of a rise-and-fall on an aEEG tracing (Fig. 4). Unlike recognition of seizures on conventional EEG, which requires trained personnel and expert interpretation by neurophysiologists,[34] recognition of seizure patterns on aEEG is presumed to be easy even for untrained personnel.

Sensitivity and accuracy are concerns in the application of aEEG to neonatal seizures. There have been several studies on the sensitivity of aEEG for an identification of neonatal seizures.[8,35-38] Shellhaas et al. investigated the sensitivity of aEEG for seizure detection by neonatologists.[35] On conventional EEG, 664 of 851 individual seizures were visible in the C3-C4 channel. These seizures were briefer, less frequent, and lower in peak-to-peak amplitude compared with conventional EEG. As a result, the neonatologists detected one or more seizures in a mean of 40.3% of the 125 records of seizures using aEEG. Shah et al. compared the accuracy of seizure detection between aEEG and aEEG plus 2-channel conventional EEG.[36] The sensitivity (27%-56%) and interobserver agreement were low in aEEG alone, compared with aEEG plus 2-channel conventional EEG. Two-channel conventional EEG identified seizures with a sensitivity of 76% and a specificity of 78%. Other studies also showed that aEEG was not highly sensitive to individual seizures.[8,37,38] Evans et al. compared aEEG and simultaneous conventional EEG in seizure detection.[1] The sensitivity for the presence of seizures by aEEG was 80% and the specificity was 50%. The proportion of infants with seizures was overestimated by aEEG. The distinction between ictal changes and artifacts is sometimes very difficult without raw EEG. These studies indicate that there are some limitations in the detection of seizures and diagnostic accuracy using aEEG alone. Despite that, aEEG is necessary for the diagnosis and monitoring of neonatal seizures, because subclinical seizures cannot be detected without EEG recordings including aEEG. Although conventional EEG is certainly the gold standard for the diagnosis of neonatal seizures, its recording and interpretation necessitates skilled clinicians and technicians. In contrast, recording and interpretation of aEEG is much easier than that of conventional EEG. Both aEEG and conven-

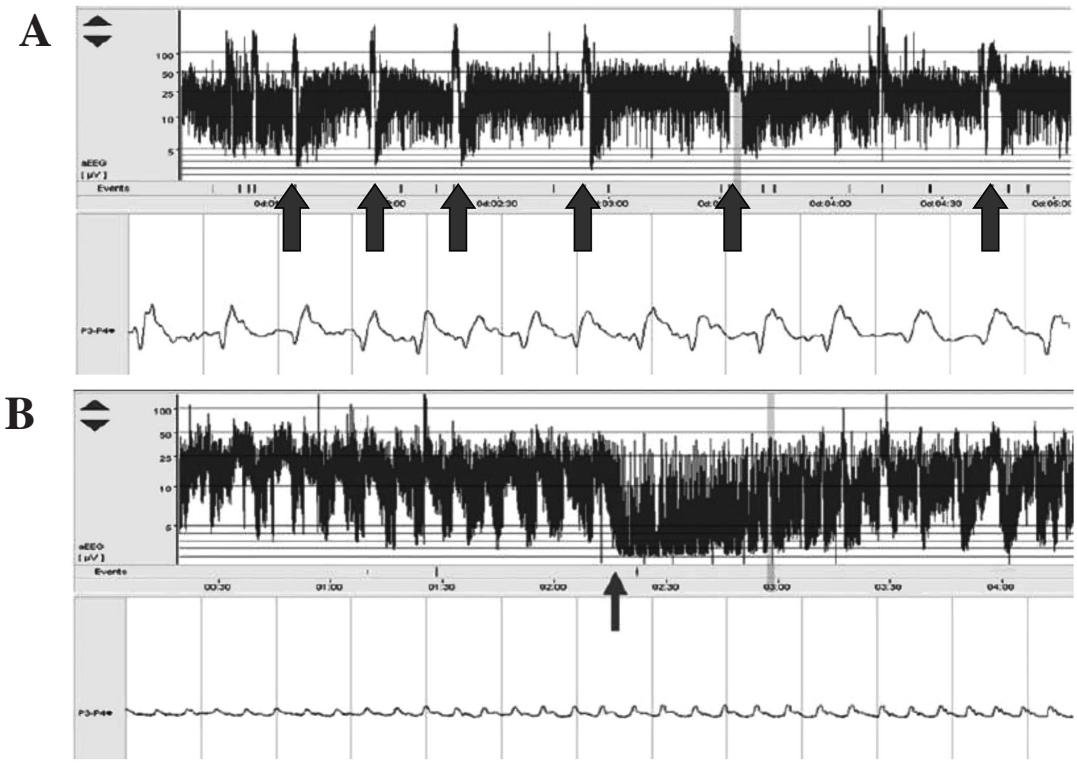

Fig. 4 Ictal changes on amplitude-integrated EEG. (A) Transient rises in the upper and lower borders are intermittently observed. A raw EEG tracing of the corresponding part shows repetitive, rhythmic and stereotyped discharges suggesting a seizure. Broad arrows indicate seizures on amplitude-integrated EEG. (B) A saw-tooth pattern with periodic repetitions of a rise-and-fall is seen on an aEEG tracing. This suggests a cluster of seizures. A narrow arrow indicates administration of antiepileptic drugs. After that, transient cessation of seizures is observed.

tional EEG should be used and the advantages and disadvantages of each modality must be understood.[39]

The treatment of neonatal seizures

Two aspects must be considered in the treatment of neonatal seizures: treatment of the seizures themselves and that for the underlying etiology. Neonatal seizures in themselves require emergency therapy, because seizures can adversely affect the long term outcome of the infant.[40,41] Moreover, etiology-specific therapy is important to prevent further brain injury. Stabilizing the general condition of the infant is necessary before starting treatment. An adequate airway and access to the circulatory system must be insured early in the course of treatment.

Etiology-specific therapy is preferred. This is particularly true for seizures associated with acute metabolic disorders including hypoglycemia and hypocalcemia, and those associated with central nervous system or systemic infections such as bacterial meningitis, septicemia, and herpes simplex infection. Rare but treatable metabolic disorders such as pyridoxine dependency, folinic acid-responsive seizures, and disorders of glucose transport should also be considered before antiepileptic treatment.[42] Unless the underlying etiology is treated appropriately, neonatal seizures will not be controlled by treatment with antiepileptic drugs. Thus, diagnostic procedures, including blood chemistry, metabolic screening, bacterial cultures, virological studies such as polymerase chain reaction, and neuroimaging, must be performed to determine the underlying etiology. Conventional EEG may alos be of help.

Treatment with antiepileptic drugs can be considered only after respiratory and circulatory support and the identification and institution of etiology-specific therapy. Seizure type (epileptic versus non-epileptic in origin) and, if epileptic in origin, seizure duration and severity should be considered before

deciding whether to initiate antiepileptic treatment. Antiepileptic drugs should be used to treat neonatal seizures of epileptic origin but not those of non-epileptic origin, as they are ineffective for non-epileptic paroxysmal events. This means that ictal EEG/aEEG recordings must be performed to determine whether the seizures are epileptic or non-epileptic before starting treatment with antiepileptic drugs.

It is not necessary to treat all neonatal seizures of epileptic origin, because some are brief, infrequent, and self-limiting. Theoretically, antiepileptic treatment is not warranted in infants with self-limiting seizures. However, it is not always easy to determine whether or not seizures are self-limiting in each individual during the first few hours after the onset of seizures. Over-treatment may occur during the acute period, especially when the seizures are associated with worsened vital signs such as bradycardia, hypotension, and desaturation. However, even in these cases, unnecessary chronic treatment with antiepileptic drugs should be avoided.

The efficacy of treatment must be evaluated by continuous EEG/aEEG monitoring. Subclinical seizures are very common after seizures with clinical manifestations are controlled by antiepileptic treatment.[6] This makes antiepileptic treatment for neonatal seizures more complicated. No one can determine the efficacy of antiepileptic treatment without continuous EEG/aEEG monitoring. For this reason, evidence of the effectiveness of antiepileptic drugs is limited.[43] Glass et al. investigated whether clinically diagnosed neonatal seizures are associated with neurodevelopmental outcomes in infants with hypoxia-ischemia after controlling for the presence and severity of brain injury seen on MRI.[44] Infants with neonatal seizures had worse motor and cognitive outcomes compared with those without seizures. They concluded that clinical neonatal seizures in infants with birth asphyxia are associated with worse neurodevelopmental outcomes, independent of the severity of hypoxic-ischemic brain injury. Kwon et al. reported opposite results.[45] They analyzed associations between neonatal clinical seizures and outcomes at 18 months of age. When adjustment was made for study treatment and the severity of encephalopathy, seizures were not associated with death, moderate or severe disability, or lower Bayley Mental Development Index scores at 18 months of life. Both of these studies had a substantial shortcoming, in that seizures were diagnosed based on clinical observation, which several studies have clearly shown to be insufficient and incorrect.[5,15] In order to clarify the effectiveness of antiepileptic drugs, studies based on continuous EEG/aEEG monitoring are essential.

It is also unclear whether or not subclinical seizures should be treated. van Rooij et al. studied whether immediate treatment of both clinical and subclinical seizures resulted in a reduction of the total duration of seizures and a decrease in brain injury on MRI.[46] The median duration of seizure patterns was 196 minutes in the group in which subclinical seizures were treated based on aEEG monitoring, compared with 503 minutes in the group in which aEEG monitoring was blinded. There was a significant relationship between the duration of seizure patterns and MRI scores in linear regression only in the latter group. They concluded that there was a trend for a reduction in seizure duration and the severity of brain injury when clinical and subclinical seizures were treated. On the other hand, Freeman stated a strong concern for application of aEEG monitoring for detection of subclinical seizures.[47] At present, the effectiveness of medications for treatment of seizures in the newborn has not been established. Therefore, the consequences of introducing automated EEG to detect subclinical neonatal seizures are likely to be similar to those seen after the introduction of fetal heart monitoring during labor: creation of another pseudodisease, followed by unwarranted intervention, and increased legal liability. Freeman warned clincians to beware of unintended consequences. The indications for antiepileptic treatment should be dependent on the etiology of neonatal seizures. Subclinical seizures of acute symptomatic origin such as hypoxic-ischemic brain injury are likely to be self-limiting and may not require additional administration of antiepileptic drugs. On the other hand, subclinical seizures due to remote symptomatic origin such as brain malformation should be treated vigorously, because these seizures can be classified as epileptic encephalopathies.

It is also unclear whether non-epileptic paroxysmal motor phenomena should be treated. Various types of these phenomena have been misdiagnosed as seizures of epileptic origin. Neonatologists may

become upset when neurologists insist that no treatment is necessary in these cases. Rationally, antiepileptic treatment is ineffective or harmful and etiology-specific therapy should be preferred. However, there are presently no conclusions on this issue.

The selection of antiepileptic drugs is also a problem. At present, there is no evidence indicating which antiepileptic drugs should be used for neonatal seizures. Phenobarbital and phenytoin are frequently used as the initial drugs worldwide. However, neither agent appears to be more effective than the other, and neither is as effective as previously thought.[48] In Japan, midazolam is also often used as the initial drug for neonatal seizures, but its efficacy has not been sufficiently evaluated.

Conclusion

The diagnosis and management of neonatal seizures are challenging issues. Electroclinical dissociation is an outstanding feature of neonatal seizures. For this reason, neonatal seizures should be diagnosed based on ictal EEG/aEEG findings and the efficacy of treatment should be evaluated using continuous EEG/aEEG monitoring. Although conventional EEG is the gold standard for the diagnosis of neonatal seizures, aEEG can be considered as an option. However, aEEG has substantial limitations. Evidence is limited on the treatment of neonatal seizures. In order to establish effective treatment, studies using continuous EEG/aEEG monitoring and long-term follow-up are necessary. Widespread use of EEG/aEEG is desirable to solve several problems in the diagnosis and treatment of neonatal seizures.

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