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NEONATAL SEIZURES: NARRATIVE REVIEW

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ABSTRACT Neonatal seizures are often complex and difficult to recognize, but can be identified through electroencephalogram (EEG) monitoring. The Brighton Collaboration has developed a scheme with five levels of diagnostic certainty to guide treatment decisions when EEG is not available. Different seizure types are usually associated with specific underlying causes, which may require specific diagnostic and treatment approaches. Neonatal seizures require prompt management, including the stabilization of cardiovascular and respiratory function and the identification of the underlying cause. EEG monitoring is considered essential for the detection of seizures and should be performed until the neonate has been seizure-free for 12 to 24 hours. Treatment involves the use of antiseizure medication and may include pyridoxine challenge or other treatment options such as the ketogenic diet, intravenous immunoglobulin, or corticosteroids if seizures are refractory to conventional antiseizure medication. It is important to differentiate between seizures and nonepileptic motor phenomena, which can occur without obvious cause or as symptoms of drug withdrawal, electrolyte abnormalities, hypoglycemia, or infection. Neuroimaging is also considered essential for the detection of possible structural abnormalities in neonates with seizures.

KEYWORDS : Neonatal seizures, EEG monitoring, Diagnostic certainty, Neuroimaging, Antiseizure medication

INTRODUCTION

Neonatal seizures, defined by the ILAE as seizures occurring within 4 weeks after birth in full-term infants or within 44 weeks of postmenstrual age in preterm infants, have an incidence of 2.29 cases per 1000 live births. Causes can be metabolic disturbances, infections, or cerebral lesions. Provoked seizures, the most common type, are transient and usually do not require long-term treatment. Hypoxic ischemic encephalopathy is the most common cause of provoked seizures in full-term neonates, while intraventricular hemorrhage is most common in preterm neonates. Neonatal epilepsy syndromes, with genetic causes, may require long-term treatment. Identifying the underlying cause is essential for appropriate management and treatment (1,2).

METHODS

A comprehensive literature search was conducted using electronic databases including PubMed, MEDLINE, EMBASE, and Cochrane Library. The search terms used were "neonatal seizures", "convulsions neonatal", "epilepsy neonatal", "diagnosis", "etiology", "treatment", "outcome", and "management". The search was limited to articles published in English between January 2000 and December 2022. Additional articles were identified through manual searches of reference lists of relevant articles. Full-text articles were reviewed for inclusion if the title and abstract suggested that the article met the inclusion criteria. The extracted data was synthesized narratively, using a thematic analysis approach.

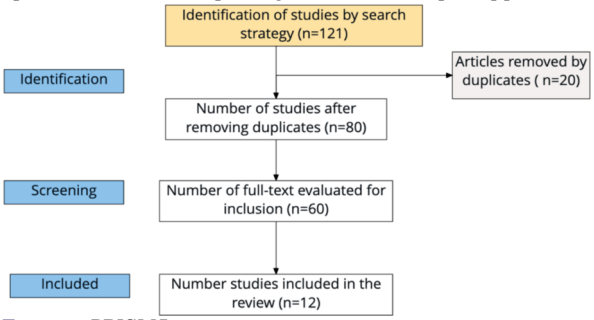

Figure 1. PRISMA.

Clinical Presentation

Neonatal seizures can be challenging to diagnose due to their complex and subtle presentation. Seizures often begin focally and then spread to the entire body, although generalized seizures are rare. Some seizures may only have an EEG component, highlighting the importance of EEG as a diagnostic tool for identifying neonatal seizures, as emphasized by the International League Against Epilepsy (ILAE) (2,3).

The Brighton Collaboration proposed a five-level scheme for diagnosing neonatal seizures when EEG is not available. Treatment is recommended for the highest level of certainty (level 1), as well as suspected events with a focal clonic or tonic feature (level 2). For suspected events that are not focal, clonic, or tonic, and when EEG is not available, there is no clear guidance (level 3). Levels 4 and 5 do not require treatment. This scheme can be applied to single or multiple seizures (3).

Seizures in neonates can have various clinical presentations, and their underlying causes may differ depending on the type of seizure. For instance, focal clonic seizures usually indicate a cerebral infarction and require imaging to confirm the diagnosis. On the other hand, tonic seizures are often associated with hypoxic ischemic encephalopathy, metabolic disorders, channelopathies, vascular disorders, or cortical malformations. Genetic causes are often involved in sequential seizures and epileptic spasms. Nonetheless, some of these associations are based on current opinion, and further studies with larger neonatal cohorts are required to confirm them. (3,4)

Certain motor phenomena, such as tremors, jitteriness, and myoclonic movements, can be difficult to distinguish from seizures in newborns. These movements can occur without an apparent cause or as a symptom of drug withdrawal, electrolyte abnormalities, hypoglycemia, or infection. These events do not have corresponding EEG patterns and are not considered seizures. When EEG is not available, the Brighton Collaboration's five-level scheme can be used to determine the likelihood of a paroxysmal movement being a seizure. Benign neonatal sleep myoclonus is a common, self-resolving condition characterized by myoclonic events during sleep with a normal EEG. Neonatal hyperekplexia is a rare disorder characterized by muscle rigidity, exaggerated startle reaction, and nocturnal myoclonus with a normal EEG and is not considered an epilepsy syndrome. The Vigevano maneuver, which involves forced flexion of the head and legs towards the trunk, can halt attacks in neonatal hyperekplexia (4).

Assessment of Neonatal Seizures

Neonatal seizures are a medical emergency that requires

prompt management. The initial management of neonatal seizures involves stabilizing cardiovascular and respiratory function, followed by identification of the underlying cause. Treatable medical abnormalities, such as hypoglycemia, hypocalcemia, and hyponatremia, must be rapidly detected and corrected, as they can lead to seizures. The detection of seizures can be confirmed by electroencephalogram (EEG) monitoring, which should be initiated as early as possible. The workup for neonatal seizures involves a thorough evaluation that includes perinatal, birth, and family histories to identify any clues to the underlying cause of seizures. A comprehensive evaluation might also include screening for neonatal infections, toxicologic testing, and metabolic testing for organic acidemias, urea cycle defects, and fatty acid oxidation defects (5).

Neuroimaging is considered essential for the detection of possible structural abnormalities in neonates with seizures. Additional imaging with axial computed tomography or, preferably, magnetic resonance imaging of the head can be performed when feasible. If a stroke is suspected, magnetic resonance angiography and venography may be indicated as part of the assessment (5,6).

Continuous EEG monitoring is the gold standard for the detection of seizures and should be performed until the neonate has been seizure-free for 12 to 24 hours. However, conventional 20-channel EEG or amplitude-integrated EEG may be used to diagnose neonatal seizures when continuous EEG monitoring is not feasible. Amplitude-integrated EEG is a readily available bedside test that is easy to apply and can be interpreted by neonatologists. However, it is less sensitive and less specific than conventional EEG for seizure detection (6).

Treatment for neonatal seizures involves the use of antiseizure medication. Pyridoxine challenge may be attempted if seizures continue despite the administration of conventional antiseizure medication. If a clear response is observed, pyridoxine administration is continued throughout the patient's lifetime. If seizures are refractory to conventional antiseizure medication, other treatment options, such as ketogenic diet, intravenous immunoglobulin, or corticosteroids, may be considered (6,7).

Treatment of Acute Symptomatic Seizures

Treatment of neonatal seizures is a critical aspect of managing neonatal care. As per the guidelines provided by the International League Against Epilepsy (ILAE), neonatal seizures should be treated promptly, regardless of the cause, to prevent further complications. Phenobarbital is the first-line antiseizure medication recommended by the ILAE, followed by levetiracetam, midazolam, lidocaine, or phenytoin as a second-line intervention if the neonate does not respond to the first medication. However, there is limited evidence on the best medication to use after phenobarbital has failed (7).

In addition to antiseizure medication, therapeutic hypothermia for 72 hours is used in neonates with moderate-to-severe hypoxic ischemic encephalopathy to reduce seizure burden and ameliorate brain injury, improving developmental outcomes. It is important to discuss the possible cause of seizures and treatment options with the family and determine the duration of treatment based on the neonate's response. If conventional antiseizure therapies fail, trials of pyridoxine, pyridoxal phosphate, and folinic acid can be considered to correct uncommon vitamin-responsive epilepsies (7,8).

Furthermore, stopping antiseizure medication should be considered only after all provoked seizures have ceased, regardless of MRI or EEG findings. However, this recommendation does not apply to neonatal-onset epilepsy syndromes, as they may remit spontaneously or be resistant to medications. In addition to the above, recent studies have suggested that other medications, such as topiramate, clonazepam, and valproate, may also have a role in treating neonatal seizures (**Table 1**). However, further studies are required to determine their efficacy and safety in this population (8).

Table 1. Treatment for Symptomatic Seizures

Medication	Loading Dose	Maintenance Dose
Phenytoin	20 mg/kg of body weight IV over 30-min period	5 mg/kg of body weight per day.
Levetiracetam	40 mg/kg of body weight IV; second loading dose 20 mg/kg	40–60 mg/kg of body weight per day.
Midazolam	0.05–0.15 mg/kg of body weight IV	1 μg/kg of body weight per minute (60 μg/kg per hour), as a continuous infusion, increased in steps of 1 μg/kg per minute; maximum dose: 5 μg/kg per minute

Prognosis and Complications

Neonatal seizures are a concerning medical condition that can have significant consequences for the long-term development of affected infants. In general, the prognosis for neonatal seizures depends on various factors, including the underlying cause of the seizures, the age at which they first occur, their duration, and the effectiveness of treatment. Early recognition and treatment of neonatal seizures are crucial to prevent adverse outcomes and improve the long-term prognosis of affected infants (9).

Research suggests that the prognosis for neonatal seizures can vary widely, depending on the underlying cause of the seizures. Self-limited epilepsy syndromes, characterized by frequent seizures, typically have a good prognosis and remit spontaneously. In contrast, developmental and epileptic encephalopathies, which result from severe, diffuse brain injury, often with a genetic cause, have a poor overall prognosis. Untreated neonatal seizures can cause hippocampal sclerosis and worsen the clinical outcome, regardless of the cause. Analyses of data from several case series suggest that status epilepticus or seizures lasting longer than 12 to 13 minutes per hour are associated with a poor outcome, independent of the cause. Studies in animals suggest that the immature brain may be less susceptible to injury from seizures than the more mature brain (10).

In a study involving neonates with hypoxic ischemic encephalopathy, normal or mildly abnormal background EEG activity was found to be predictive of a normal developmental outcome (11). Further research is needed to identify additional factors that may influence the prognosis of neonatal seizures (12).

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