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Review Article

Neonatal Convulsions

Nawal Abood Bahassan[1]*, Marwah Ali Al Hausa[2], Eyad Mansour Alghamdi[3], Yassmin Hussain Alabndi[4], Jhayer Talat Tunsi[2], Sami Ayyadah Alshammari[5], Suhaib Ghazi Refae[6], Hanan Adem Mohamed Nur[6], Afaf Abdulali Alsubhi[6], Abdulrahman Hilmi Sindi[6], Mousa Ali Alhaddad[7] and Rayan Ali Karbouji[8]

[1]*Consultant of Pediatric Neurology, East Jeddah General Hospital, Jeddah, Saudi Arabia*

[2]*East Jeddah General Hospital, Jeddah, Saudi Arabia*

[3]*Al-Baha University, Al Baha, Saudi Arabia*

[4]*Mansoura University, Egypt*

[5]*University of Hail, Hail, Saudi Arabia*

[6]*Maternity and Children's Hospital, Jeddah, Saudi Arabia*

[7]*Maternity and Children's Hospital, AlAhsa, Saudi Arabia*

[8]*Prince Mohammad Bin Abdul Aziz National Guard Hospital, Al Madinah, Saudi Arabia*

***Corresponding Author:** Nawal Abood Bahassan, Consultant of Pediatric Neurology, East Jeddah General Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: Neonatal seizures or neonatal convulsions are fits that can occur from birth to the end of the neonatal period. The most vulnerable period for developing seizures is first 1 - 2 days to the first week after delivery. The seizures in neonatal period constitute a medical emergency which often leads to serious malfunction of or damage to immature brain and is called for a neurological emergency demanding an immediate diagnosis and management. Subtle seizures are the most common ones and myoclonic seizures to be the worst one to occur in neonatal period. Multiple etiologies are known to be associated with neonatal seizures, with hypoxic-ischemic encephalopathy to be the most common one. Other causes such as hypoglycemia, hypocalcemia and meningitis should be ruled out and treatment should be initiated accordingly.

Aim of the Study: The aim of the review is to understand the etiology and management of neonatal seizures.

Methodology: The review is the comprehensive research of PUBMED since the year 1987 to 2013.

Conclusion: The immature brain seems to be more prone to seizures than the more mature and developed brain. That is why seizures are more common in neonatal period than during any other time of life. Seizures are also most common neurological emergency, reflect serious underlying emergency and are associated with high mortality and morbidity. EEG is gold standard for monitoring seizure and establishing diagnosis. Phenobarbitone is the first choice of medication internationally. It is effective in 50% of cases but prolonged use may be harmful thus the treatment should be initiated according to the etiology associated. Major focus should be on parents' concerns regarding the short-term and long-term outcome. Abundant animal models show that seizures themselves disrupt the developing brain and thus there is an urgent need to develop safe, accurate and widely available method for identifying and treating neonatal seizures.

Keywords: *Neonatal Seizure; EEG; Anti-Epileptic Drugs*

Introduction

Clinically, a seizure is defined as paroxysmal alteration in neurologic function i.e. motor, behaviour, autonomic function. The incidence of seizure in infants born is 0.5 to 3 per 1000 live births and incidence is given higher in preterm infants ranging from 1 - 13% with lower birthweight. The majority of neonatal seizures occur on the first day and 70% of all cases have been diagnosed by fourth day of birth [1,2].

Infants with neonatal seizure are at higher risk of neonatal death or neurological impairment and epilepsy disorder in later life. Although, mortality due to neonatal seizures has decreased over the years from 40% dropped to 20%, the prevalence of long-term neurodevelopment sequelae largely remained unchanged at 30%. The possibility behind this could be improper and inadequate management of seizures [3].

Methodology

As systematic search was conducted regarding most available evidence discussing the Neonatal convulsions. We have used PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant available and accessible articles were reviewed and included. The terms used in the research were: Neonatal seizure, classification of seizures, EEG, anti-epileptic drugs.

Classification and characteristics of neonatal seizures

Type	Characteristics	Ectal EEG Abnormality
Subtle (Most common type, 50% of all seizures)	Ocular-tonic horizontal deviation of eyes or sustained eye-opening with ocular fixation, Oro-facial-lingual movements- chewing, tongue thrusting, lip-smacking, limb movements- cycling, paddling, boxing jabs, Autonomic phenomena -s tachycardia and bradycardia, Apnoea	Variable
Clonic	Repetitive jerking, distinct from jittering. Unifocal or multifocal	Common
Myoclonic	Rapidly isolated jerks, focal, multifocal or generalized	Common if generalized, uncommon if focal
Tonic	Stiffening, decerebrate posturing. Focal or generalized	Common if focal and uncommon if generalized

Table 1: *Classification of seizure by Volpe.*

Type	Characteristics	Epileptic Origin
Focal clonic	Rhythmic muscle contraction	✓
Focal tonic	Sustained posturing of limb or trunk	✓
Myoclonic	Random single contraction	✓
Spasms	Flexor or extensor in clusters	✓
Electrographic	No clinical correlate	✓
Generalized tonic	Sustained symmetric posturing	-
Motor automatism	Ocular, oro-facial-lingual or progression movement of limbs.	-

Table 2: *Classification of seizure by Mizrahi and Kellaway.*

Etiology of neonatal seizures

As per recent studies, the most common cause of neonatal seizures are hypoxic-ischemic encephalopathy, metabolic disturbances, and meningitis but the incidence of intraventricular haemorrhage was low in both studies [8,9]. However, the etiology varies in different patient population, level of monitoring, etc.

Hypoxic-ischemic encephalopathy (HIE)

HIE secondary to perinatal asphyxia is the most common cause of neonatal seizures which is about (50 - 65%). The seizures due to HIE mostly starts within the first 12 hours of life and the rest manifest by 24 - 48 hours of age. In perinatal asphyxia, additional problems such as hypoglycemia, hypocalcemia, intracranial hemorrhage may co-exist which should always be excluded. Post HIE subtle seizures are the most common one to occur [6-9].

Metabolic causes

The metabolic causes of seizures include hypoglycemia, hypocalcemia and hypomagnesemia. In rare case pyridoxine deficiency and inborn error metabolism (IEM) may cause neonatal seizure [6-9].

Infection

Meningitis should be excluded in all neonates. Meningoencephalitis secondary to intrauterine infection (TORCH group, syphilis) may also present as seizures in the neonatal period [6-9].

Intracranial haemorrhage

Seizures in neonates due to subarachnoid, intraparenchymal and subdural hemorrhage occur very often. Seizure secondary to intraventricular haemorrhage occurs more commonly in preterm infants. Seizures due to intracranial hemorrhage mostly occur between 2 to 7th day of age. While seizures occurring on 2 - 3 day of life is often due to subarachnoid haemorrhage [6-9].

Developmental defects

Some rare cause of neonatal seizures is cerebral dysgenesis and neuronal migration disorders [6-9].

Other causes

The other causes for neonatal seizure include polycythemia, maternal narcotic withdrawal, drug toxicity such as theophylline and doxapram, local anesthesia injection into scalp which is suspected in presence of unilateral fixed and dilated pupil, phacomatosis such as tuberous sclerosis, incontinent pigment. Low zinc levels in CSF fluid may lead to multifocal clonic seizure on 5th day of life (benign idiopathic neonatal convulsion) [6-9].

Management

Approach to an infant with neonatal seizure starts with history, examination, and further investigations to rule out the cause [1,6,7].

History: A complete description of seizure should be obtained from parents or attendant. Eye movements change in skin colour, limbs movements, whether or not infant was sleeping or conscious at the time of seizure. The day of life on which the seizures occurred provide important information for appropriate diagnosis. Intrauterine infection, maternal diabetes, and narcotic addiction should be elicited in antenatal history. Perinatal asphyxia is common cause of neonatal seizure so a detailed history of fetal distress, decreased fetal movement, instrumental delivery should be elicited, as use of mid-cavity forceps while delivery is associated with accidental injection of local anesthesia in the scalp which can precipitate neonatal seizures. Apart from this, feeding and family history should also be useful. Inborn errors in metabolism (IEM) and consanguinity of parents may be one of the reasons for neonatal seizure [1,6,7].

Examination: It includes [1,6,7]:

- General examination: Birthweight and any obvious malformation or dysmorphic feature.
- Systemic examination: Hepatosplenomegaly or abnormal urine odor may be suggestive of IEM, skin examination may show hypopigmented macules or ash-leaf spot suggestive of tuberous sclerosis.
- Vital signs: Heart rate, respiration, blood pressure, capillary refill time and temperature should be recorded.
- CNS examination: Bulging of anterior fontanel may be suggestive of meningitis or intracranial bleeding. Neurological examination may include the assessment of consciousness, tone and fundus examination.

Investigation

Majority differential diagnosis can be made using detailed history. The investigation should be focused on common aetiologies requiring prompt specific treatment. Following investigations are included to exclude the other etiology associated with neonatal seizure [10]:

- Septic screen: Blood culture and lumbar puncture.
- Laboratory test: Assessment of glucose, blood gas, electrolytes, packed cell volume, bilirubin, ammonia, metabolic screening, TORCH (Toxoplasmosis, rubella, CMV, herpes), screening for drug abuse by mother.
- A therapeutic trial of pyridoxine and pyridoxal phosphate.
- Cranial ultrasound scanning, MRI.
- EEG.

Neuroimaging

Cranial ultrasound is useful in first-line imaging investigation for exclusion of gross CNS pathologies such as CNS malformation or periventricular haemorrhage. In case the ultrasound examination is normal, and infant continues to have seizure then CT or MRI is carried out to detect pathology such as cerebral infarction, subdural and subarachnoid haemorrhage [10].

Electroencephalography (EEG)

EEG plays an important role in the diagnosis of neonatal seizure and differentiating it from non-epileptic events. Paroxysms are considered to be seizure if they last more than 10 seconds. A neonatal electrographic seizure is often not sustained, and the typical duration of seizure is 2 - 3 minutes. But many seizures can be shorter particularly in preterm infants. The neonatal seizure has a focal onset whereas generalized onset spike and wave seizure discharge is extremely rare. Neonates can display simultaneous independent focal electrographic seizures [10,11].

Ictal EEG may be useful in the diagnosis of seizure in muscle-relaxed infants. It should be carried out as soon as the infant is stable enough to be transported for EEG and done preferably within first week for at least 1 hour.

Amplitude integrated EEG is the new method for monitoring cerebral electrical activity at the bedside. aEEG is useful in evaluating and identifying seizure activity in neonates. Seizure activity on aEEG is characterized by rapid rise in both the lower and upper margins of trace but focal or relatively brief seizure are missed by this technique [4].

Initial medical management

The first step in the management of seizure is to nurse the baby in thermoneutral environment and ensuring the airway, breathing, and circulation. Oxygen should be administered and IV access should be secured. Blood collected for glucose and other investigation. Correction of hypoglycemia and hypocalcemia, if the glucose shows hypoglycemic state. 2 ml/kg of 10% dextrose should be given as bolus injection followed by continuous infusion of 6 - 8 mg/kg/min and if the calcium shows hypocalcemia treatment with 10% calcium gluconate (100 mg/kg or 1 mL/kg IV) followed by 8 ml/kg/d infusion.

If seizure continues then 0.25 ml/kg of 50% magnesium sulfate is given intramuscularly [4].

Anti-epileptic drug therapy (AED)

AED should be considered if the seizure persists after correction of hypocalcemia/hypoglycemia.

Phenobarbitone

It is first-line AED and drug of choice in treatment of neonatal seizure. The ideal dose is 20 mg/kg/IV slowly over 20 minutes if seizure persists then loading dose of 10 mg/kg can be used every 20 - 30 minutes until a total 24-hour dose of 50 mg/kg has been given. The maintenance dose is 3 - 5 mg/kg/day in 1 - 2 divided doses, started 12 hours after the loading dose. There is evidence that phenobarbitone increases the electroclinical dissociation, while the number of electroclinical seizure decreases, the number of electrographic seizure increases [4,12,13].

Phenytoin

Phenytoin along with other benzodiazepine is second line AED. Phenytoin is proven to cause significant myocardial depression and should be avoided in babies requiring inotropic support. If used it is indicated when the maximal dose of phenobarbitone fails to resolve seizure. The dose is 20 mg/kg IV at a rate of not more than 1 mg/kg/min under cardiac monitoring. It should be diluted in normal saline. A repeat dose of 10 mg/kg may be tried in refractory seizure. The maintenance dose is 3 - 5 mg/kg/d (maximum of 8 mg/kg/d) in 2 - 4 divided doses. To avoid the myocardial depression, prodrug fosphenytoin can be used which has high water solubility and less likely to cause soft-tissue injury when compared to phenytoin. The ideal dose is 1.5 mg/kg [4,14].

Benzodiazepine

This group of drugs is required in 15 - 20% of neonatal seizure. The commonly used drugs are lorazepam (0.05 mg/kg IV bolus over 2 - 5 min), clonazepam (0.1mg/kg iv/30 min), midazolam (0.15 mg/kg IV bolus followed by infusion of 0.1 to 0.4 mg/kg/hr). diazepam is usually avoided in neonates due to its shorter duration of action, narrow therapeutic index, and presence of preservative sodium benzoate. And thus, lorazepam is preferred over diazepam. On comparison midazolam is faster acting than lorazepam and it causes less respiratory depression and sedation compared to lorazepam. Clonazepam achieves a better EEG control. Midazolam has shorted half-life than clonazepam and does not accumulate and it avoids the side effect of increases oropharyngeal secretion [4,15].

Other drugs used for maintenance therapy or refractory seizure are as follow [4].

Lidocaine

Initial bolus dose (2 mg/kg over 10 minutes), followed by a continuous infusion of 7 mg/kg/hour for 4 hours and decreasing the dose by 50 percent every 12 hours with maximum infusion time preferable less than 30 hours [16].

The side effects may include arrhythmias, hypotension, and seizures. Thus, it should strictly not administered with phenytoin.

Paraldehyde

It is used in seizures refractory to first-line drugs such as phenobarbitone. The given dose is 0.1 - 0.2 ml/kg/dose may be given IM, or 0.3 ml/kg/dose mixed with coconut oil in 3:1 via rectal route. An additional dose may be given after 30 minutes and q 4 - 6 hourly. The side effects include pulmonary hemorrhage, pulmonary edema, hypotension and liver injury.

Sodium valproate

Used as maintenance therapy in neonates and can be used as IV dose in acute condition with a dose of 20 - 25 mg/kg/d followed by 5 - 10 mg/kg every 12h. Side effects are hepatotoxicity.

Vigabatrin

Used for refractory seizures, for infantile spasms. Dose is 50 mg/kg/day.

Topiramate

Because of its potential neuroprotective effect against injury caused by seizures it has shown the promising result in neonatal seizures and refractory infantile spasms. Requires higher initial maintenance dose of 3 mg/kg.

Conclusion

Neonates are prone to seizures due to immature underdeveloped brain with variable clinical manifestation. There is multiple etiologies associated with neonatal seizure, their presence is often first sign of neurologic dysfunction and that are powerful predictors of long-term cognitive development impairment. The initial assessment is done through a detailed clinical history and examination which gives a clue of underlying cause and helps in diagnosis the appropriate etiology. Apart from neuroimaging and metabolic screening, routine laboratory test and specialized test for IEM, EEG remains the gold standard. Amplitude-integrated EEG is convenient and useful bedside tool. Used drug therapy is anti-epileptic drugs and benzodiazepine. While there is increasing evidence of harmful effect of seizures on developing brain, there is also evidence that commonly used medication is potentially neurotoxic in animal models. Thus, research and development in newer agents would reduce such possibility and provide long term efficacy.

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