Common Causes of Neonatal Seizure among Neonates Admitted to Neonatal Care Unit at Al Ramadi Teaching Hospital for Maternity and Children

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KEYWORDS
neonatal seizure, Etiology, AL Ramadi west of Iraq.

ABSTRACTs
Neonatal seizures are the transient occurrence of signs and symptoms due to an abnormal excessive or synchronous neuronal activity in the neural cells causing paroxysmal electro clinical changes. Neonates are at high risk for seizures as compared to other age groups.
The aim of this study was to identify the common causes that lead to neonatal seizure during the period from first of October 2020 to the end of July 2021using history, physical examination, and investigations in Al Ramadi teaching hospital for maternity and children. The total number of neonates diagnosed as neonatal seizure during the period of study in Al Ramadi teaching hospital for maternity and childhood was 64 cases. Total number of admissions to neonatal care unit was 4102 so the prevalence in neonatal care unit was 15.6 per 1000 live births. 30 (47.1 %) cases were diagnosed as perinatal asphyxia, 18 (28 %) cases were diagnosed as metabolic, 6 (9.4 %) cases were diagnosed as infections, seizures, 4 (6.3%) cases were diagnosed as intracranial hemorrhage, 3(4.6%) cases were diagnosed as CNS malformation, while 3 cases (4.6 %) were Unknown etiology. 38 (59.3%) of studied neonatal seizures were male, while 26 (40.7%) were female. Male to female ratio was (1.4:1). 37 (57.8%) were term babies (≥37 gestational age), while 27 (42.2%) were preterm babies (<37 gestational age). 41 (64%) of studied neonatal seizure cases were born by normal vaginal delivery, while 23 (36%) of cases were born by caesarian section delivery. The most common cause of neonatal seizure was perinatal asphyxia followed by metabolic causes then infection, intracranial hemorrhage, CNS malformations and unknown causes. Male are more common than female. In term neonates more common than preterm and in normal vaginal delivery more than cesarean section.

1. Introduction

Neonatal seizure

Definition

Neonatal seizures are the transient occurrence of signs and symptoms due to an abnormal excessive or synchronous neuronal activity in the neural cells causing paroxysmal electro clinical changes. [1]

Background

Neonates are at higher risk for seizures as compared to other age groups . [2] The high risk for seizures is multifactorial and often caused due to the relative excitability of the developing neonatal brain and the high risk for brain injury due to hypoxia-ischemia, stroke, and intracranial hemorrhage.[3]

The estimated rate of seizures in term newborns is approximately 1 to 5 per 1000 live births.4However, population based studies take no notice of

The low diagnostic accuracy of diagnosis by clinical observation alone, and gold standard prolonged, continuous video electroencephalogram

(cEEG) monitoring is not widely available enough to make population-based predictions; therefore the true incidence remains unspecified .[5, 6]

The differential diagnosis for neonatal seizures is broad and includes structural, genetic, and metabolic causes. Seizures that arise from an acute symptomatic cause, such as hypoxic-ischemic encephalopathy, infection, transient metabolic disturbance, stroke, or intracranial hemorrhage, are much more common than neonatal onset epilepsies, which may be due to prior injury, malformation, or genetic causes. Rare conditions such as inborn errors of metabolism and vitamin-responsive epilepsies must be considered in the setting of refractory seizures. [7, 8]

Neonatal seizures are high risk for early death. Cognitive and motor disabilities, and epilepsy are common. [9]

The outcome depends largely on the underlying cause and severity of brain injury. The effect of the seizures themselves is not known, although studies in animal models suggest that seizures can alter brain development, leading to deficits in memory, learning, and behavior. [10]

Pathophysiology

There are several factors that are specific to the neonatal brain that lead to increase excitability and seizure generation, poor response to standard treatment, and adverse effect on brain development. [11]

There are number of mechanisms that make the immature brain more excitable in comparison to the brain of other age groups. [11, 12]

1-The neonatal period is a time of physiologic, use dependent synaptogenesis, and both synapse and dendritic spine density are at their top. [13]

2- Glutamatergic neurons, the primary excitatory mechanism of both the developing and adult brain are abundant, and their receptors are shaped with subunits that allow relative hyper excitability. [14, 15]

3-Gammaaminobutyricacid (GABA), while it is the primary inhibitory mechanism of the adult brain can due to the preponderance of the NKCC1 and delayed expression of the KCC2 chloride transporters, which lead to a high intracellular chloride concentration and depolarization in response to GABAergic agents.[16–18]

Immature development of the excitatory and inhibitory neurotransmitter systems leads to a lack of good targets for ordinary anti-seizure medications, which makes neonatal seizures particularly difficult to treat. The immature brain may be resistant to medications that act as GABA agonists, not only as a result of the paradoxical chloride gradient but also due to overall lower receptor expression and an immature subunit composition that is less sensitive to benzodiazepines than the brain of other age groups.[11,12]

Seizures and Early Brain Development :Although early work with animal models reveal that the developing brain is more resistant to seizure-induced necrosis than the adult brain, more recent work has shown that early-life seizures can affect the developing brain though by altering neuronal circuitry, which can result in impaired learning and memory and enhanced susceptibility to epilepsy later in life.[10]

Animal models of early life seizures show developmental alterations that can include reduced density of dendritic spines in hippocampal pyramidal neurons; decreased neurogenesis; delayed neuronal loss; and changes in hippocampal plasticity such as decreased capacity for long-term potentiation, reduced susceptibility to kindling, and enhanced paired-pulse inhibition. [19]

Human studies in children with hypoxic ischemic injury show an independent association between seizures and impaired brain metabolism, and poor long-term neurodevelopmental outcome. [20]

Causes of neonatal seizure

Hypoxic-Ischemic Encephalopathy (HIE):. This is the most common cause of neonatal seizures, accounting for 50–60% of patients. [21]

Vascular causes : these include ischemic strokes and intracranial bleeds and occur in about 10–20% of patients. [22]

Intracranial Infections occur in about 5–10% of the cases of neonatal seizures. Neonatal sepsis may be categorized as early-onset neonatal sepsis

(EONNS) and late-onset neonatal sepsis (LONNS) which is defined as

Illness appearing from birth to 7 days, eight to 28 days postnatal age

respectively. [23]

Brain Malformations it represents about 5–10% of neonatal seizure cases.[22]

Metabolic Disturbances[24] include

-Hypoglycemia it occurs in small neonates and in prediabetic or diabetic mother.

-Hypocalcaemia happened with two peaks. The first peak occur to low birth weight infants in the first 2-3 days of life. The second peak occurs in large, full term babies later in neonatal life who consume milk that

has high ratio of phosphorus to calcium and phosphorus to magnesium.

-Hypomagnesaemia is usually occurs in combination with hypocalcaemia.

-Hyponatremia usually secondary to water intoxication or inappropriate antidiuretic hormone secretion.

Local anesthetic intoxication seizures. [25]

amino acid or organic acid metabolism defect.[26]

Pyridoxal dependency disorders These seizures, which are often multifocal clonic, usually begin in the first few hours of life. [25]

Drug Withdrawal like narcotic analgesics, sedative–hypnotics, and others usually started in the first 3 days of life. [25]

benign neonatal convulsions (5th-day fits), which often apneic, and focal motor seizures that begin usually in the 5th day of life.[25]

benign familial neonatal seizures autosomal dominant start at 2-4 days of life and usually remit at 2-15 wk of age. The seizures consist of tonic posturing, eye deviation, clonic jerks, and sometimes motor automatisms. [25]

Early myoclonic encephalopathy and early infantile epileptic encephalopathy (Ohtahara syndrome). [21]

MANAGEMENT

The overall management goal for neonatal seizures is to rapid and accurately identify, and stop electrographic seizures, while determining the most likely underlying cause.

Neonatal seizures are often the first sign of neurologic problem and are often an indication of serious underlying brain injury.[27,28,29] Therefore, a suspicion of seizures in a newborn should be treated as a neurologic emergency and treated immediately , and prompt rapid evaluation to identify the cause, as well as emergent medical management to stop seizures should be performed while preventing secondary injury by maintaining physiologic temperature, oxygenation, blood pressure, glucose, and ventilation.[30]

Seizure diagnosis

Clinical diagnosis of seizures is approximately 50% accurate for events detected at the bedside. Additionally, clinical detection requires constant observation by the medical staff and even so will fail to detect seizures with no or very subtle clinical correlate (e.g., subtle, clonic movements that are covered by the infant's blanket or eye deviation). Subclinical seizures are the most seizures in neonates, especially in severe brain injury, and in children who have received seizure medications. [31]

Initial evaluation of a neonate with suspected seizures should also focus on rapid determination of the cause. Emergent evaluation of serum glucose and risk factors for infection is an important first step, because bacterial meningitis and hypoglycemia can lead to permanent injury if left untreated.[32]

Detailed history and physical examination are important to assess for risk factors of neonatal seizures.

Investigations: CBC, RBS, serum calcium, serum magnesium, serum potassium, serum sodium, serum chloride, RFT, LFT, CSF examination and septic screen

Amplitude-integrated electroencephalography (aEEG; a simplified bedside neurophysiology tool that can be applied and interpreted by neonatologists, nurses, or medical Care Nursery side staff) is used or replace cEEG in a variety of centers.

Conventional cEEG [33]

1-Gold standard for seizure detection

2- For monitoring neonates with paroxysmal events and/or at high

Risk for seizures

3-Recommended by the American Clinical Neurophysiology Society

aEEG

1- Lower specificity and sensitivity than cEEG[34]

2- Hundred Percent sensitivity for status epilepticus[35]

3- Lowest sensitivity for seizures those are focal, brief, and distal

From recording electrodes[36]

4-Raw EEG tracing helps to differentiate artifact from seizure [37]

5-Experienced readers perform better than nonexperts [38]

Clinical evaluation

1-Accuracy approximately 50% [6]

2- Most seizures will not be identified (subclinical or indefinite

Seizures) [31]

Additional evaluation, including genetic testing, ammonia, serum amino acids, lactate, urine organic acids very-long chain fatty acids, and sulfites, and cerebrospinal fluid studies for glucose, glycine, lactate, and neurotransmitters, as well as additional testing for inborn errors of metabolism may be needed on a case by case basis, especially in the setting of seizure refractory to medical treatment and seizure of unknown cause. [39]

Cranial ultrasound is important for rapid initial assessment of a sick neonate to identify large space occupying lesions, such as hydrocephalus, hemorrhage, arteriovenous (AV) malformations, but is insensitive for global and focal hypoxic-ischemic injury, especially in the days after insult. [40]

magnetic resonance (MRI) is essential to identify underlying injury or developmental abnormalities and to help clinicians and the family to better understand the prognosis.[41]

CT-scan (Computed tomography) is used for appropriate diagnosis of acute causes of seizures. [42]

Pharmacological treatment

There are no evidence based guidelines for the pharmacologic treatment of neonatal seizures. [43, 44] Opinion supports use of pharmacologic treatments with a goal of stopping electrographic seizures, even those without clinical seizure. [45]

However, evidence is deficit regarding the relative benefit versus potential side effects of anticonvulsants used to treat neonatal seizure, many of which can lead to neuronal apoptosis in animal models. [46]

Although data are absent regarding optimal treatment guide for neonatal seizures, experts' advice rapid administration of an adequate loading dose of medication because acute symptomatic seizure burden is highest at the onset, [47] and patients with little number of seizures are easier to treat. [46]

Similarly, experts' advice treatment of both clinical and subclinical

Seizures given similar pathophysiology and the only difference between the 2 may be slight anatomic differences in their cortical distribution. [45]

Aim of the study:

The aim of this study is to identify the common causes that lead to neonatal seizure among neonates admitted to neonatal care unit at Al Ramadi teaching hospital for maternity and children.

2. Patients and methods

Study Design, Data Collection and Time Setting

A cross sectional study done for neonates admitted to neonatal care unit in Al Ramadi teaching hospital for maternity and childhood from a period from the first of October 2020 to the end of July 2021.

Study patients

All neonates (age 28 days or less) admitted as neonatal seizure was included in this study. Seizure was suspected by history from a person who cares of the neonate or witnessed and confirmed by clinical observation by doctors in the neonatal care unit and detailed history, physical examination and investigations. Neonates were considered

preterm if gestational age less than 37 weeks

And term for more than 37 weeks from last menstrual period or first ultra sound. Gestational age assessment using new Ballard score. Low birth weight was considered for neonate with birth weight less than 2.5 kilograms

Data collection

For all studied cases, a special prepared paper for each neonate to list an information which will be taken from the families including;

1. Age at which the seizure happen. (During first week or more than first week).

2. Gender.

3. Birth weight (<2.5 kg or ≥ 2.5 kg).

4. Type of labor (normal delivery or cesarean section).

5. Gestational age. (<37 week, ≥37 week).

6. Type of seizure

7. Perinatal history

Prenatal: history of hypertension, diabetes, fever, smoking, alcohol consumption, and drug exposure.

Natal: type of delivery, type of anesthesia if cesarean section, any complications during surgery.

Post natal: need NCU admission or not, order of baby in family and health state of sibling, and any similar condition in the family

8. Occipito- frontal circumference (OFC) was measured

9. Apgar score was recorded in the resuscitation room for in born neonates

A list of investigation was done for neonates suspecting of having seizure to support the history and clinical examination in order to reach to the final diagnosis including;

1. Serum calcium, glucose, and electrolyte. (Hypocalcaemia when serum calcium level < 7.0 mg/dl

Hypoglycemia when blood glucose level < 40 mg/d. hypomagnesaemia when serum magnesium level < 1.5 mg/dl. Hyponatremia when and serum sodium level < 130 mEq/L).

2. CSF examination.(cell count and differentiation, protein, sugar , CSF culture) .

3. Chest x-ray.

3. Septic screen: Complete blood count (CBC) , general urine exam(GUE) , urine culture, C-reactive protein(CRP) , blood culture.

5. Total serum bilirubin

4. Ultrasound examination of brain , CT scan and MRI for suspected patients with congenital anomalies or hemorrhage .

EEG not available.

Inclusion citeria

All neonates with age 28 days or less who diagnose as having seizure

Exclusion criteria

1-neonatal jitterness

2-families who refuse the study

3-tremor

4-tetanus neonaturm

5-kernictus

6-benign sleep myoclonus

7-startle disease

8-tonic posturing

Ethical approval

Permission and Informed consent was obtained from the parents or family member, provide full explanation about the objectives of the study. Approval from the Arab Board of Health Specialization

And from AL Ramadi teaching hospital for maternity and children

Statistical Analysis

Data collected were checked for accuracy and completeness and were coded and entered into the Statistical Package for Social Sciences (SPSS), Descriptive statistics for all studied variables and Chi-squared test were used and P-value level <0.05 was considered significant throughout the study.

3. Results

The total number of neonates diagnosed as neonatal seizure during the period of study in Al Ramadi teaching hospital for maternity and childhood was 64 case, and the total number of admission was 4102 so the prevalence of neonatal seizure in NCU was 15.6 per 1000 live births.

Thirty 30 (47.1 %)cases were diagnosed as perinatal asphyxia , 6 (9.4 %) cases were diagnosed as infections, 18 (28 %) cases were diagnosed as metabolic seizures (9 hypoglycemia, 8 hypocalcaemia, 1 hyponatremia), 4 (6.3%) cases were diagnosed as intracranial hemorrhage, 3(4.6%) cases were diagnosed as CNS malformation, while 3 cases(4.6 %) were Unknown etiology. Figure 1

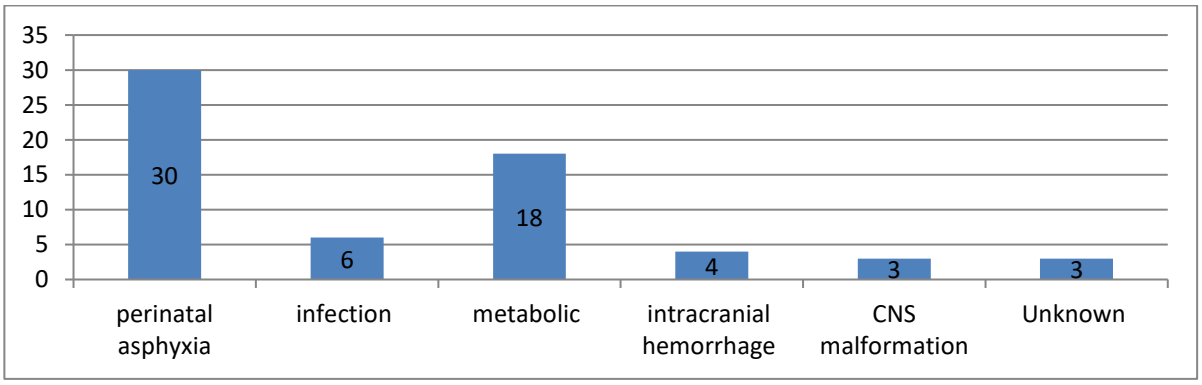

Figure1. Distribution of diagnosed neonatal seizures according to the cause.

Most of diagnosed neonatal seizures were from subtle type 36(56.2 %), followed by multifocal clonic 13(20.4 %), clonic 7(10.9%), tonic 6 (9.4 %), and the least was myoclonic 2 (3.1%). Figure2.

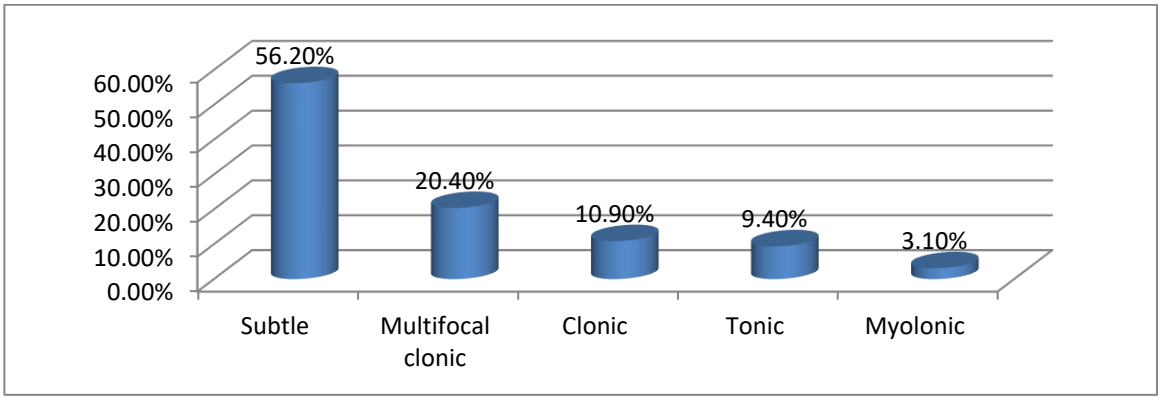

Figure 2. Distribution of cases according to type of fit.

Thirty eight 38 (59.3 %) of studied neonatal seizures were male, while 26 (40.7 %) were female. Male to female ratio was (1.4:1). Table 1

Table 1 Distribution of cases according to gender.

Type of seizure	Male	Female	Total	P-value
Perinatal asphyxia	19	11	30	0 .14
Infection	4	2	6	0.41
Metabolic	8	10	18	0. 63
CNS malformation	3	0	3	0.083
Unknown	2	1	3	0 .56
Intracranial hemorrhage	2	2	4	1
Total	38(59.3%)	26(40.7%)	64(100%)	-

Forty two 42(65.6%) studied neonate with seizure had a birth weight less than 2.5 kg (LBW), while 22 (34.4%) had a birth weight more than 2.5 kg . Table 2.

Table 2. Distribution of cases according to birth weight.

Type of seizure	<2.5kg	>2.5kg	Total	P-value
Perinatal asphyxia	21	9	(n = 52;	0 .06
Infection	4	2	6	0 .41
Metabolic	10	8	18	0.63
CNS malformation	2	1	3	0 . 56
Intracranial hemorrhage	2	2	4	1
Unknown	3	0	3	0.083
Total	42(65.6%)	22(34.4%)	64	-

Thirty seven 37 (57.8%) were term babies (≥37 gestational age), while 27 (42.2%) were preterm babies (<37 gestational age).Table 3.

Table 3.Distribution of cases according to gestational age.

Type of seizure	≥37 GW	<37 GW	Total	P-value
Perinatal asphyxia	20	10	30	0 .068
Infection	1	5	6	0.102
Metabolic	11	7	18	0 .34
CNS malformation	0	3	3	0.083
Intracranial hemorrhage	3	1	4	0.31
Unknown	2	1	3	0.56
Total	37 (57.8%)	27 (42.2%)	64	-

Fifty two 52 (81.2%) of studied neonatal seizure cases were diagnosed during first week of neonatal age, while 12 (18.8%) cases were diagnosed after the first week of neonatal period. Table 4.

Table 4 Distribution of studied cases according to time of seizure.

Type of seizure	First week fit	After first week	Total	P-value
Perinatal asphyxia	29	1	30	< .00001
Infection	1	5	6	0.102
Metabolic	15	3	18	0 .004
CNS malformation	3	0	3	0 .083
Intracranial hemorrhage	3	1	4	0.31
Unknown	1	2	3	0.56
Total	52(81.2%)	12(18.8%)	64	-

Forty one 41 (64%) of studied neonatal seizure cases were born by normal vaginal delivery, while 23 (36%) of cases were born by caesarian section delivery. Table5.

Table 5. Distribution of studied cases according to mode of delivery.

Type of seizure	Normal vaginal	caesarian section	Total	P-value
Perinatal asphyxia	21	9	30	0.028
Infection	3	3	6	1
Metabolic	11	7	18	0 .34
CNS malformation	1	2	3	0 .56
Intracranial hemorrhage	4	0	4	0.045
Unknown	1	2	3	0.56
Total	41 (64%)	23 (36%)	64	-

4. Discussion

In this study, males 38(59.3%) with neonatal seizures were more than females 26(40.7%) with same condition; indicating that male neonates had a higher risk of seizures. Consistent with Inaam Mohamed, et al 2020 study reports that 65.5% were males and 34.3% were females, and nearly similar to the study conducted by Sedighi M et al concluded that male babies were more than females (58% male , 42% female).[48,49]

Approximately half of neonates in current study (n = 30; 47.1%) suffering seizures due to perinatal asphyxia representing a major etiological risk, 28% due to metabolic seizures (hypoglycemia, hypocalcaemia, hyponatremia), and 9.4% due to infection; consistent with Dinesh Das, et al 2016 study reported that birth asphyxia was the most common cause of neonatal seizures (64, 56%), followed by neonatal meningitis and metabolic disorders. [50]

Similarly; a study in Iraq (Al-Momen H et al) was conducted recently found that birth asphyxia was the commonest cause of neonatal seizures in (n = 81;40%) followed by infections in (n = 77;37.9%), then metabolic factors in (n = 52; 25.6%. [51]

While Islam MN, et al 2016 reported 78% of neonates have hypoxic ischemic encephalopathy [52]

In contrast, Inaam Mohamed, et al 2020 [48] reports that the most common cause of seizures was neonatal encephalopathy and infections.

According to the gestational age of neonates, in current study seizures among term neonates were more frequent than that in preterm, (n=37; 57.8%) for term verse (n=27; 42.2%) for preterm). This is similar to the Inaam Mohamed, et al 2020 [47] concluded that majority of neonates who developed seizures were delivered at term (7.2% as compared to 3.1% in preterm), and in contrast with Carlotta Spagnoli et al, 2018 reported that the prevalence of seizures in preterm newborns is higher than in full-term ones (22.2% compared to 0.5%).[53]

This study agree with Essam J. Al-Zwaini et al , 2006 which done in the same hospital of our study which show that (38.7%)of neonatal seizure cases were preterm and (61.3%) full term.[54]

Based on our result, we estimated that 81.2% of the neonates had first attack of seizures within the first week of life mostly due to birth asphyxia. Similar to our finding, Rachna Pasi, et al 2019 reported that early onset (up to 7 days of life) of seizures was seen in 94.7% of neonates [55] and Fateme Eghbalian, et al 2015 reported that 78% of neonatal seizures happened in the first days of life [56] may be due to delivery conditions and hypoxia. Therefore, we can reduce the incidence of neonatal seizure by improvement of obstetric care.

It was obvious that 65.6% of neonates in this study have birth weight less than 2500 g, which indicated that seizures may be more common in infants with lower birth weights opposite to Fateme Eghbalian, et al 2015 [56] reports that 24% of neonates had less than 2500 gr weight suggested that seizures could be more common in infants with heavier birth weights. The most common type of seizures in the observed study was subtle 56.2% followed by multifocal clonic in 20.4%, and clonic in 10.9%. Baudou E, et al 2019 found that the main type of seizure was focal clonic in 35%, followed by multifocal clonic in 24%, and subtle in 20%. [57] Another study found that focal clonic was the common type of seizures among 25.1% of neonates, and subtle seizures were reported in 19.8% by Inaam Mohamed, et al 2020, [56] this was similarly reported by Islam MN et al. [48,52]

Normal vaginal delivery was the commonest type of delivery in this study (among 64% of neonates with seizures); in significances with perinatal asphyxia and intracranial haemorrhage. Similarly, study by Lawgali AMS et al 2019 reported that 67% of neonates with seizures were delivered vaginally and most of them with birth asphyxia.[58]

Another study by Hyun Sook Hong & Ji Ye Lee, 2018 demonstrate that cesarean section is associated with a reduced risk of intracranial hemorrhage in comparison with high risk of vaginal delivery, where 71.4% of neonates with intracranial hemorrhage delivered vaginally. [59]

5. Conclusion

The most common cause of neonatal seizure is perinatal asphyxia followed by metabolic causes. It is more common in male than female and more common in term than preterm. Also it is common in low birth weight neonate. Subtle type of seizure more common than other types followed by multifocal clonic . Neonates delivered by normal vaginal delivery are more likely to develop seizure than neonates delivered by cesarean section.

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