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Original Research Article

ETIOLOGY AND SHORT OUTCOME OF NEONATAL SEIZURES IN BABYLON GYNECOLOGY AND PEDIATRICS TEACHING HOSPITAL

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Abstract

Background: Neonatal seizures are the most common manifestation of neurological disorders in the newborn period and an important determinant of outcome.

Objectives: To determine the etiology and immediate outcome of seizures among neonates admitted to Babylon Gynecology and Pediatrics teaching hospital.

Method: this is prospective, observational study was conducted in the neonatal care unit and general wards of Babylon Gynecology and Pediatrics teaching hospital. The study was done from 1st of April 2014 to 1st of October 2014.All the neonates developing clinically identifiable seizures before 28 days of life were enrolled in the study. Seizure etiology was based on positive clinical data, laboratory findings, and /or imaging studies of the brain (ultrasonography, CT. Scan, or MRI).

Results: Among the 3154 neonates admitted to the neonatal care unit and general wards during the study period, 122 (3.9%) neonates (term and preterm) developed clinical seizures. The most common cause of neonatal seizures was hypoxic ischemic encephalopathy 41(33.6%) of 122 neonates, followed by metabolic disturbances collectively constitute 36(29.5%) neonates, infections was found in 20 (16.4%) neonates. Other important etiological factors include intracranial hemorrhage, hyperbilirubinemia encephalopathy (Kernicterus), brain malformation and unknown causes each accounted for 13(10.7%), five (4.1%), five (4.1%) and two (1.6%) respectively. The outcome were, death 21 (17.2%) neonates, 32(26.2%) neonates were discharged with neurological sequelae, while 69 (56.6%) neonates discharged with no sequelae.

Conclusion: Hypoxic Ischemic Encephalopathy was the most common cause of neonatal seizure. The two most common diagnosis associated with neonatal seizure that carry worse mortality and neurological sequelae were neonatal Hypoxic Ischemic Encephalopathy and infections

Keyword: neonatal seizures, etiology, outcome.

Introduction

Neonatal seizure is the commonest neurological dysfunction in the neonatal period; it is a paroxysmal alteration in neurological function like motor, behavior and /or autonomic function[1] and can occur at any gestational age [2]. The neonatal central nervous system is particularly susceptible to seizures due to a combination of enhanced excitability, and low levels of the inhibitory neurotransmitter gamma-amino butyric acid (GABA)[3]. Neonatal seizures are dissimilar to those in a child or adult because generalized tonic-clonic convulsion don't occur during the first month of life that is due to the arborisation of axons and dendritic processes as well as myelination is incomplete[4]. The most common seizures type in neonatal are focal or multifocal clonic, tonic, myoclonic, and subtle[5].The subtle seizures comprise a variety of motor and autonomic phenomena [6]. The incidence rate of clinical seizures varies from approximately 1.1 to 8.5 per 1000 live births, with higher incidence in premature and low birth weight neonates [4]. It may be up to 3.4% of neonatal intensive care unit admission[6].

The major causes of neonatal seizures are Hypoxic-Ischemic Encephalopathy (HIE), which represents about 50% of the causes of neonatal seizures. Metabolic abnormalities, infection, intracranial hemorrhage, developmental anomalies[7,8], and others like inborn errors of metabolism are a rare causes of neonatal seizures. They are extremely important to consider as their detection allows appropriate genetic counseling and may permit specific therapy [9]. The causes of seizures in preterm neonates is different from that seen in term neonates, where the HIE is the most frequent cause in term neonates, followed by cerebral malformations and metabolic disturbances , while in preterm neonates interventricular hemorrhage and infections are the most frequent causes[10]. Intrauterine infection caused by cytomegalovirus is the most common of the intrauterine infections that affect the central nervous system and leading to brain atrophy with sever neurological sequelae [11]. Neonates with seizures are at risk of death, whereas survivors are at risk of neurological sequelae, developmental delay, later epilepsy and cognitive impairment so, we need to initiate an early diagnostic work up to determine the causes, depending upon the facilities available [12]. However, electroencephalograph (EEG) provides a useful non-invasive diagnostic tool of neonatal seizures and evaluates degree of perinatal brain damage. Nevertheless, its interpretation is influenced by variations is normal maturation process of brain. also not all seizures can be picked by surface recorded EEG and many clinically silent electrographic seizures have been reported[13],this electro-clinical dissociation more common in neonates than in other age groups[14],that can result in either over or under–estimation of the incidence of neonatal seizures[15].

A team of neonatologists, neuropaediatricians, laboratory specialists, neurophysiologists and radiologists facilitates the adequate care of the neonates [16]. The advancement in the treatment of neonatal seizures has changed little compared to seizures in the older children. Phenobarbital remains the drug of choice especially in resource-poor settings [17], while in developed countries neurocritical care for neonate is a growing multidisciplinary subspecialty, for example, therapeutic hypothermia may reduce morbidity and mortality in neonates with HIE[18]. Mortality following seizures has improved in the last decade especially in full term babies, but the prevalence of adverse neurodevelopmental sequelae remains relatively stable, therefore, the aim of the study was to determine the incidence rate,

etiological factors, and short-term outcome following neonatal seizure in Gynecology and pediatrics teaching hospital.

Patients and methods

This prospective, observational study was conducted in the neonatal care unit and general wards of Babylon Gynecology and Pediatrics teaching hospital. The study was done from first of April to the first of October 2014. The entire neonate who developed clinically identifiable seizures before 28 days of life was enrolled in the study. Baseline characteristics of convulsive neonate, including gender, gestational age, and weight were recorded at admission. A detailed antenatal history, which included history of maternal illness during pregnancy like preeclampsia, diabetes mellitus, choriaminitis, and abruption placenta, natal history labor records for evidence of fetal distress and Apgar score, type of delivery, were recorded on a predesigned forma. The diagnosis of neonatal seizures based on clinical observation, and accurate description of the type of seizures according to the classification of Volpe[(5)], into subtle, multifocal clonic, focal clonic, and myoclonic, and time of onset of seizures were recorded. Family history of seizures or neonatal death recorded. A complete clinical examination of neonates, blood glucose, total serum calcium and magnesium levels were done immediately after neonate had seizure and before starting of any specific treatment. The seizure etiology diagnosis was based on positive clinical data, laboratory findings, and/or brain imaging studies (ultra-sound, CT scan, MRI). Various criteria for diagnosing metabolic abnormalities were defined as hypoglycemia; blood sugar <40mg /dl (2.2mmol/L), hypocalcemia; total serum calcium <7.0mg/dl (1.7mmol/L), hypomagnesaemia; serum magnesium <1.5mg/dl, hyponatremia; serum sodium <135mEq/L and hypernatremia when it is >150mEq/L.

The diagnosis of HIE was based on history, physical examination, Apgar score, arterial blood gas, and neuro-imaging. Diagnosis of neonatal infection was based on the clinical manifestation, sepsis workup, and positive blood culture. Bacterial meningitis was confirmed by positive CSF culture. Intracranial hemorrhage and brain malformation was determined by brain CT, ultrasound, and MRI. Kernicterus diagnosed by high total serum bilirubin and TORCH infection by serological tests.

Statistical analysis; the extracted data were analyzed using SPSS software package version 21. Frequencies, cross tabulation and Chi square test were used for analysis of data, P value <0.05 was considered significant.

Results

Among the 3145 neonates admitted to the neonatal care unit and general wards during the study period 122 (3.9%) neonates (term and preterm) developed clinical seizures.78(63.9%) neonates were male and 44 (36.1%) were female. The male /female ratio was (1.77:1). 111 (91.0%) neonates were term, whereas only 11 (9.0%) neonates were preterm. The mean $\pm$ SD of birth, weight was (3148$\pm$717) gm. 107(87.7%) neonates were above 2500gm, and 15 (12.3%) neonates were below 2500gm.The mode of delivery in 80 (65.6%) neonates were normal vaginal delivery (NVD) and in 42 (34.4%) neonates were cesarean section (CS).

We found that 12 (9.8%) neonates were born to mother who had history of preeclampsia , 6 (4.9%) neonates mothers had history of diabetes mellitus (DM) , choriaminitis was observed in 3 (2.5%) neonates , abruption placenta in 4 (3.3%) neonates , 10 (8.2%) neonates had family history of neonatal seizures and 6 (4.9%) neonates with history of neonatal death .(table1)

Table 1: Demographic characteristics of neonates with seizure.

Characteristics		No. of neonates	Percentage
Gender	Male	78	63.9
	Female	44	36.1
Birth weight	<2500	15	12.3
	.2500	107	87.7
Gestational age	Term	119	91.0
	Preterm	11	9.0
Mode of delivery	NVD	80	65.6
	CS	42	34.4
Maternal disease	Preeclampsia	12	9.8
	Diabetes mellitus	6	4.9
	Chorioamnionitis	3	2.5
	Abruption placenta	4	3.3
Family history	Seizure	10	8.2
	Neonatal death	6	4.9

We found that 37 (30.3%) neonates had first seizure before 24 hours, 25 (20.5%) neonates had developed seizure between 24 and 72 hours , i.e. (50.8%) neonates had early onset seizure (before72 hours). In addition, 60 (49.2%) neonates after 72 hours (late onset). (Table 2)

Table 2: The time of onset of seizures

Onset type	Time of onset	No. of neonates	percentage
Early onset	< 24 hours	37	30.3
	24 to 72 hours	25	20.5
Late onset	> 72 hours	60	49.2
Total		122	100

We noticed that the most common cause of neonatal seizures was HIE 41(33.6%) of 122 neonates, followed by metabolic disturbances collectively constitute 36 (29.5%): 21(17.2%) of them were due to hypocalcemia, 10 (8.2%) were

due to hypoglycemia, 2 (1.6%) were due to hyponatremia, 1 (0.8%) was due to pyridoxine deficiency and one had inborn error of metabolism (Galagtocemia).Infection was found in 20 (16.4%) neonates, septicemia was the commonest cause 11 (9.0%) neonates, meningitis 6 (4.9%) neonates, and TORCH infection three (2.4%) neonates (two neonates had Cytomegalovirus, and one had Toxoplasmosis infection). Other important etiological factors include intracranial hemorrhage, hyperbilirubinemia encephalopathy (Kernicterus), brain malformation and unknown causes each accounted for 13 (10.7%), five (4.1%), and two (1.6%) of seizures respectively. (Table 3, 4)

Table3: Etiology of neonatal seizures.

Etiology	No. of neonate	percentage
Hypoxic ischemic encephalopathy	41	33.6
Metabolic abnormalities	36	29.5
Infection	20	16.4
Intracranial heamorrhage	13	10.7
Kernicterus	5	4.1
Brain malformation	5	4.1
Unknown	2	1.6
Total	122	100

Table 4: The metabolic etiological disorders of seizures

Metabolic disorder	No. of neonates	Percentage of total etiologies
Hypocalcemia	21	17.2
Hypoglycemia	10	8.2
Hyponatremia	2	1.6
Hypomagnesaemia	1	0.8
Pyridoxine deficiency	1	0.8
Inborn error of metabolism	1	0.8
Total	36	29.5

The relation of onset to the etiological conditions was examined and we found early onset seizures significantly associated with this set of conditions (P- value=0.001).

Hypoxic-ischemicencephalopathy and brain malformations seem the strongest predictors of early onset seizure. (Table 5)

Table 5: The relation of seizures onset time to etiological disorders.

Etiological disorder	Early onset (< 72 hours)		Late onset (>72 hours)		Total	
	No.	%	No.	%	No.	%
Hypoxic/ischemic encephalopathy	34	82.9	7	17.1	41	100
Infection	4	20.0	16	80.0	20	100
Intracranial haemorrhage	5	38.5	8	61.5	13	100
Metabolic disorders	15	41.7	21	58.3	36	100
Kernicterus	00	00	5	100	5	100
Brain malformation	4	80.0	1	20.0	5	100
Unknown	0	00	2	100	2	100
Total	62	50.8	60	49.2	122	100

Fisher Exact Test =35.92 df=6 P-value=0.001

The common type of seizures observed were subtle type 46 (37.7%) neonates followed by tonic type 35 (28.7%), clonic 32 (26.2%) and myoclonic types nine (7.4%).

Table 6: Types of neonatal seizures.

Type of neonatal seizure	No. of neonates	Percentage
Subtle	46	37.7
Tonic	35	28.7
Clonic	32	26.2
Myoclonic	9	7.4
Total	122	100.0

The mortality were 21 (17.2%) neonates, 32 (26.2%) neonates discharged with sequelae, and 69 (56.6%) neonates were discharged with no sequelae. table7

Table 7: The outcomes of neonatal seizures.

Outcomes	No. of neonates	Percentage
Discharged with no seqaelae	69	56.6
Discharged with seqaelae	32	26.2
Death	21	17.2
Total	122	100

The outcome of neonates with seizure according to etiological factors were the highest death in neonates with HIE (6/21), followed by infection 4, metabolic three, brain malformation 3, intracranial haemorrhage 2, sever kernicterus 2, and unknown cause one neonate. (Table 8). Brain malformation was cerebral dysgenesis, holoprosincephaly, hydrocephaly with meningomylocele.

Table 8: The outcomes according to etiological disorders

Etiology	**No. & %**	**Outcome**		
		Discharged with no sequelae	**Discharged with sequelae**	**Death**
Hypoxic/ischemic encephalopathy	41 (33.6)	26	9	6
Metabolic abnormalities	36 (29.5)	30	3	3
Infection	20 (16.4)	7	9	4
Intracranial haemorrhage	13 (10.7)	4	7	2
Kernicterus	5 (4.1)	1	2	2
Brain malformations	5 (4.1)	0	2	3
Unknown	2 (1.6)	1	0	1
Total	122 (100.0)	69	32	21

Discussion

We found that the incidence of neonatal seizures was 3.9% , which is comparable to the finding of Al-Zawini et al[6]study (3.4%), but lower than the results of Sahana et al [4] study (8.38%), Sabzehei et al [7] study (9.1%) and Mwaniki et al [17] study (9.0%) .This low incidence might be due to that our

study was done at neonatal care unit and general wards of the hospital; however, their study reflects the frequency of seizures in established intensive care units, which is high 10-25% in the neonatal intensive care units [19]. In addition, we were only able to document seizures that were clinically obvious. It is possible that we missed subclinical seizures, because no EEG facilities in the hospital, in addition the Mwaniki et al study [17] study was done in rural area hospital in Africa with high incidence of infection.

In our study, the seizures are common in neonates more than 2500gm weight; this is comparable with Sahana et al [4] study. In addition, the incidence appears to be less in preterm neonates; this may be due to high mortality rate in preterm, due to other complications like severe respiratory distress. The majority of neonates who developed seizures were full term 111 (91%) neonates, which is comparable to the finding of Al-Marzoki (95.4%) [8] And Yaser [20] study (93.1%) was full term. The seizures were more common in the male neonate (63.9%) which goes with Sahana et al[4] study (52.29), Sabzehei et al[7] study (57%), Al-Marzoki[8] (54.5%), and Yaser [20]study (53.4%)

We found that 62 (50.8%) of the neonates had seizure of early onset (before 72 hours) .This is similar to finding of Sahana et al[4] study , Sabzehei et al[7] study, and Fiaz et al study [19] who found that 77.9% , 50% , 59.6% of neonate, respectively , had early onset seizures. While Al-Marzoki[8]find that most neonatal seizure of late onset (after 72 hours), this difference could be explained by that most common cause for seizure in our study was due to HIE, but the most common dominant factor contributing to neonatal seizures in Al-marzoki study was metabolic abnormalities.

The most common cause of neonatal seizure in the current study was HIE 41 (33.6%) followed by metabolic abnormalities 36 (29.5%) . this finding is comparable to studies by Sahana et al[4] study , and Kumar et al[13] study , respectively, 57.8% and 44.4% of the neonates with HIE followed by 15.5% and 23.33% of neonates with metabolic abnormalities. Amar et al [22]study, also found asphyxia was the most common cause (42.7%), followed by metabolic abnormalities(20%).Sabzehei et al[7] study results shows that HIE 34.3% was the most common cause followed by infections in 24.5% of neonates, while the main diagnosis in Mwaniki et al[17] study were sepsis in 85 (60%) then neonatal encephalopathy in 30(21%).Al-Marzoki [8] found that metabolic abnormalities 42(47.7%) neonates then birth asphyxia represent the second most common cause in his study 14(15.9%) neonates.

In the present study the infections were in 20 (16.4%) neonates which is similar to Sahana et al [4] (14.6%), and Legido et al [21] (17.2%) of neonates. While Sabzehei et al [7] study, Takande et al [23] study and Fiaz et al study reported high infections rate 24.5%, 28.2%, and 28.7% of neonate respectively. This may be a reflection of early use of antibiotics in our neonatal care unit.

Other important etiological factors of neonatal seizure include intracranial hemorrhage 13 (10.6%) of neonates, which is similar to Bushra et al [24] (9.5%) and Sabzehei at el [7] (6.9%). The most common metabolic disturbances were hypoglycemia and hypocalcemia, which is consistent with the observations of Sabzehei et al study and Fiaz et al [19] study.

In our study, hypoglycemia in 10(8.2%) neonate, hypocalcemia was observed in 21(17.2%) neonate. 15 of them developed seizures on second and third postnatal day. Hypocalcemia occurs in preterm neonates, those with HIE and infants of mothers with DM. Sahanaa et al [4] study reported hypoglycemia in 10 (9.17%) and hypocalcemia in seven (6.42%) neonates. Kumar et al[13] study found the incidence of

seizures due to hypoglycemia in his study was (11.11%) and hypocalcemia was observed in (10) neonates. the study conducted by Kumar et al[13] study and Al-Marzoki[8] showed that biochemical abnormalities were seen in neonates with HIE , intracranial hemorrhage, infection and metabolic abnormalities. Kumar et al [13] study reported that perinatal asphyxia was the most common cause of neonatal seizure, the exact contribution of hypoglycemia and hypocalcemia as a cause of seizure in neonates with perinatal asphyxia is not certain. Moreover, Al-Marzoki [8] also demonstrated that hypocalcemia and hypoglycemia were most common metabolic abnormalities. The above results were comparable with finding of our study.

In this study the most common type of seizure was subtle (37.3%), followed by tonic (28.7%), clonic (26.2%), and myoclonic (7.4%). Similar results were described by Sabzehei et al[7] and Al-Marzoki [8], but this were different from Sahana et al [4] study and Kumar et al[13] study in which clonic seizures was the most common (44.9% and 42.2% respectively).

The outcomes of the neonates with seizures in our study were, 69(56.6%) neonates had discharged without sequelae, 32(26.2%) neonate had neurological sequelae, and 21 (17.2%) neonates had died. This is comparable to finding reported by Sahana et al[4] study (49.54%) neonates had recovered completely, (32.11%) of neonates had neurological sequelae, (18.35%) of neonates died. However, it was higher than that (14.7%) reported in the study of Sabzehei et al [7].This increased mortality may be due to the severity of the etiological factors in the neonate of our study, but not recorded in Sabzehei et al [7]. Where three of death with severe brain malformation, cerebral dysgenesis, holoprosencephaly, hydrocephaly and two neonates with sever Kernicterus. Other causes of mortality in our study were HIE and infection, both represent the highest number of death among the neonates with seizure. The results of outcome in our study was comparable to the range of mortality recorded by Uria-Avellanal et al [25] (range: 7-16%) and the range of neurodevelopmental sequelae (range; 27-55%). The true relation between etiological factors and outcome cannot be ascertaining during this short period of study and immediate outcome, further long term follow-up study is recommended.

Conclusion:

-the most common cause of neonatal seizure was HIE

-subtle seizure represents the commonest type of neonatal seizure

-Hypoglycemia and hypocalcemia are the most common transient metabolic abnormality seen in neonates with seizure, the best outcome was observed with them.

-The two most common diagnosis associated with neonatal seizure, that carry high mortality and neurological sequelae were neonatal HIE and infections, which both of them are preventable.

Recommandations

-Recognition of etiological factors is helpful in treatment and prognosis

-Metabolic abnormalities should be ruled out and treated if present

-Improvement of antenatal services and obstetrical care with regular monitoring of fetal heart rate to ensure safe delivery and appropriate neonatal resuscitation-

-Improvement of neonatal intensive care unit

-Improvement of the laboratory investigations to diagnose inborn error of metabolism

-We recommend Prospective study on the long-term neurological and developmental outcome following neonatal seizures.

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