

## Original Article

# Causes and Outcome of Acute Symptomatic Neonatal Seizures -Neonatal Care Units - Khartoum - Sudan

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## Keywords

• Neonatal; Seizures; Semiology; Causes

## Abstract

The aim of this study is to classify neonatal seizures using seizure semiology and identifying the underlying causes and the immediate outcome of seizures among neonates admitted in NICU- Khartoum-Sudan. The study included all neonates with seizure admitted to NICU at three main hospitals in Khartoum-Sudan. One hundred and sixteen neonates were enrolled in the study. Data was collected using designed questionnaire with emphasis on history, physical examination, investigations, management and outcome of seizure.

Out of 1500 neonates admitted to NICU in the study area 116(7.7%) had seizures as a major presenting symptoms. Forty eight neonates (41.4%) had hypoxic ischemic encephalopathy, Twenty six (22.4%) had evidence of septicemia/ meningitis and primary biochemical abnormalities accounted for 32(27.6%). The most common seizure type was generalized tonic clonic in 51 (44%) followed by 30(25.9%) had focal clonic. Eighty nine (76.7%) neonates were well controlled , 26(22.4%) were partially controlled and one (0.9%) neonates had poorly controlled seizures .Neonates whose mothers had illnesses related to pregnancy , neonates with generalized seizures, preterm delivery, seizures started in the first 24 hours of life and neonates with abnormal brain image, had poorly controlled seizures.

Facilities for Neonatal resuscitation, prevention of Birth Asphyxia and safe deliveries are mandatory at all levels of health care systems.

## ABBREVIATIONS

AEDs: Anti-Epileptic Drugs; PIH: Pregnancy Induced Hypertension; HIE: Hypoxic Ischemic Encephalopathy; EEG: Electroencephalogram

## INTRODUCTION

Acute seizures are one of the most common neurological disorders in newborns who require admission to the neonatal intensive care unit [1]. In general seizures occur more often in the neonatal period than at any other time of life; during this period, they most often occur within the first week of life [2]. Seizures in the neonate have unique clinical features when compared with those of older infants and children. These differences are based upon age-dependent mechanisms of epileptogenesis, the degree of brain development at seizure onset, evolution of brain involvement during the seizure, and the relative importance of non-epileptic mechanisms of seizure generation in this age group [3]. Historically, there have been a number of clinical classifications of neonatal seizures. Each, in succession, have added to the understanding of neonatal seizures and enhanced accuracy of diagnosis [4,5]. Different classification schemes have emphasized various features such as clinical manifestations only, the relationship between clinical seizures and electrical

seizure activity on the Electroencephalogram (EEG), and seizure pathophysiology [6]. Due to unavailability of EEG facilities in our setup, we here classify neonatal seizures using seizure semiology and identifying the underlying causes and the immediate outcome of seizures among neonates admitted in NICU- Khartoum-Sudan.

## MATERIALS AND METHODS

This is a descriptive cross sectional - hospital based study, conducted during the period from April to September 2019. It included all neonates with seizure admitted to NICU at Gafer Ibn ouf Specialized Hospital for Children (out-born neonates only), Soba University Hospital (in-born neonates only) and Saad Abualela Maternity Hospital (In and out-born neonates). One hundred and sixteen neonates were enrolled in the study. Data was collected using designed questionnaire with emphasis on history, physical examination, investigations, management and outcome of seizure.

## INVESTIGATIONS

All neonates enrolled in the study had initial investigations which include; Hb level, Random Blood Glucose (RBG), Serum (Calcium, Magnesium, Sodium, and Potassium). Cranial Ultrasound and / or Brain Computed Tomography (CT) and other investigations were done when deemed appropriate.

## Diagnosis

The clinician on charge made the final diagnosis after review of the admission history, inpatient management notes and laboratory investigations. For the purpose of this study we classified the etiology into main four categories; neonatal encephalopathy and hypoxic ischemic encephalopathy, structural brain injuries, Primary metabolic disturbances and CNS or systemic infections. Of note that the metabolic disturbances associated with CNS infection and HIE were not included.

## Seizures classification

Seizures were classified according to their motor manifestations into (focal clonic, multifocal clonic, generalized tonic, myoclonic, and subtle). The 'subtle' semiology refers to seizures with signs such as abnormal eye movements, lip smacking, swimming or pedaling movements, or apnea. Nurses and junior doctors are trained on non-seizure events and normal newborn behaviors as it to be excluded.

## Management

All neonates with suspected sepsis/meningitis received empirical antibiotic treatment awaiting blood cultures and CSF analysis results. Change of antibiotics and the duration of treatment were guided by the results of culture and the clinical response. There were no facilities to identify viral causes of Meningoencephalitis at our setup.

All neonates were managed according to the local protocol for seizure treatment. Decision about management was decided by the working team at NICU which include neonatologist, pediatric specialist, registrars and paramedical staffs.

## ETHICAL APPROVAL

Ethical clearance was issued from Sudan Medical Specialization Board (SMSB) ethical and research committee unit. Written informed consents were obtained from caregivers.

## DEFINITIONS

### Neonate

For the purpose of this study, we defined a neonate as any child admitted aged 28 days or younger [23].

### Seizures

Is defined as reported or observed repeated involuntary muscle contractions, abnormal tonic extensions or jerky movements of any part of the limb, face or mouth that was not stimulus sensitive or repetitive abnormal chewing, ocular or pedalling movements.

### Neonatal sepsis

Was considered as the possible diagnosis in any newborn presenting with any one of the following signs: abnormal temperature ( $>37.5^{\circ}\text{C}$  or  $<35.5^{\circ}\text{C}$ ) and multiple skin pustules, umbilical redness or pus, respiratory distress, lethargy, seizures or feeding problems

### Meningitis

Was defined as positive CSF culture or a white cell count of  $>50/\mu\text{L}$  in CSF or a positive bacterial antigen test or gram stain.

## Prematurity

Was considered in any neonate born before 37 completed weeks.

## Neonatal encephalopathy

Was considered in any newborn who had history of a poor Apgar score ( $<7$ ) at 5 min (if delivered in hospital) with accompanying history and signs such as poor cry, feeding problems, restlessness, agitation, hypotonia, hypertonia, seizures and coma, or similar symptoms and signs after excluding other possible causes for the home-birth admissions.

**Hypokalemia** was defined as plasma  $\text{K}^{+}<3.0$  mmol/L

**Hyperkalemia** as  $\text{K}^{+}>5.0$  mmol/L

**Hyponatremia** as  $\text{Na}^{+}<125$  mmol/l

**Hypoglycemia** was considered in any child with a blood glucose  $<3$  mmol/L.

## RESULTS

Out of 1500 neonates admitted to NICU in the study area 116(7.7%) had seizures as a major presenting symptoms. Nine hundred and sixty (64.0%) neonates were delivered at term of whom 69 (7.2%) had seizures. Five hundred and forty (36.0%) neonates were preterm (with mean gestational age of  $(33.5 \pm 2.5)$  weeks) of whom 17 (3.1%) developed seizures.

Twenty seven (23.3%) mothers had medical problems related to pregnancy, of whom ten mothers (8.6%) had pregnancy induced hypertension (PIH), five (4.3%) Diabetes Mellitus (DM), four (3.4%) premature rupture of membranes, three (2.5%) peripartum haemorrhage and three (2.5%) had iron deficiency anemia.

Seventy six (65.5%) were males and 40 (34.3%) were females. Twenty eight (24.1%) neonates were delivered by emergency caesarian section, 16 (13.8%) elective caesarian section and six (5.2%) neonates were delivered by forceps. Sixty nine (59.5%) neonates had evidence of birth asphyxia. Sixty (51.7%) neonates had the first attack of seizure within the first 24 hours, 46(39.7%) in the first week of life (1-7days), nine (7.8%) in (7-14) days and one (0.9%) within (15-21) days.

Five (4.3%) neonates had a sibling with neonatal seizures. Eighty eight (75.9%) neonates their birth weight was more than 2500 gm., 24(20.7%) between 2499-1499gm, four (3.4%) between 1500-1000 gm. Nine (7.7%) neonates had head circumferences (HC) below 3rd centile for age, 105(78.7%) between 3<sup>rd</sup> -97<sup>th</sup> centile and three (2.6%) their HC was above 97<sup>th</sup> centile.

Twelve (10.3%) neonates had congenital anomalies and 12(10.3%) had dysmorphic features.

Sixty (51.7%) neonates had high level of CRP, 12(10.3%) had low Hemoglobin, Seven (6.0%) had Low RBG, 18(15.5%) had low serum calcium, two (1.7%) had low magnesium and five (4.3%) had hypernatremia.

Cranial Ultrasound was done for 12 neonates of whom nine (7.8%) had dilated ventricular system and one (0.9%) had intraventricular haemorrhage. Computed Tomography of the

brain was done to nine (7.8%) neonates and revealed features of hypoxia in one (0.9%) while others were normal. Nine patients had MRI of the brain; three (2.6%) had intracranial hemorrhage, three (2.6%) had hydrocephalus and two (1.7%) had periventricular leukomalacia.

Forty eight neonates (41.4%) had hypoxic ischemic encephalopathy of whom six (5.2%) had evidence of intracranial haemorrhage. Twenty six (22.4%) had evidence of septicemia/ meningitis. Primary biochemical abnormalities accounted for 32(27.6%) of whom 18(15.5%) had hypocalcaemia, seven (0.6%) hypoglycemia, five (4.3%) Hyponatremia and two (1.7%) Hypomagnesaemia. Six (5.2%) neonates had congenital hydrocephalus; two of them are associated with meningocele. Two (1.7%) neonates had brain abscess and one (0.9%) neonate developed features of kernicterus (Table 1).

The most common seizure type was generalized tonic clonic in 51 (44%), 30(25.9%) had focal clonic and 22(19.0%) had focal tonic seizures. Twenty three (19.8%) neonates had subtle seizures type of whom 14(12.1%) had ocular phenomena, 15(12.9%) oral Phenomena, four (3.4%) autonomic features and three (2.6%) had fragmentary body movements. Fourteen (12.1%) had multiple seizure type (Table 2).

The majority of neonates 20(71.4) with generalized tonic seizures had hypoxic ischemic encephalopathy (p- value =0.01),

while the majority of neonates 17 (65.3) with subtle seizures had primary metabolic causes (0.001). There is no significant statistical correlation between other type of seizures and underlying causes (Table 3).

Ninety three (80.1%) neonates developed status epilepticus, all were fully recovered on Midazolam, Phenytoin/Phenobarbitone infusion, and none of them needed intubation and mechanical ventilation.

Ninety (77.6%) neonates received one AED, 11(9.5%) two drugs, and 15 (12.9%) were on polytherapy. The most commonly used AED was Phenobarbitone in 106(91.4%) neonates followed by Levetiracetam 48 (41.4%), Clonazepam 29 (21.5%) and four (3.4%) received Pyridoxine.

Eighty nine (76.7%) neonates were well controlled (no seizures for at least 5 days before discharge), 26(22.4%) were partially controlled (had seizures (1-5tims) during the last 5 days before discharge) and one (0.9%) neonates had poorly controlled seizures (more than 5 seizures/ 5 days before discharge).

Neonates whose mothers had illnesses related to pregnancy, neonates with generalized seizures, preterm delivery, seizures started in the first 24 hours of life and neonates with abnormal brain image, had poorly controlled seizures; which was found to be statistical significant(P- value 0.001,0.006, 0.009,0.01,0.001)

**Table 1:** Causes of neonatal seizures.

Underlying causes	Number (%)
1. Hypoxic-ischemic encephalopathy	48(41.4)
2. CNS or systemic infections (Meningitis/septicemia)	26 (22.4)
3. Primary Metabolic causes	32(27.6)
Hypocalcaemia	18 (15.5)
Hypoglycemia	07 (6.0)
Hyponatremia	05 (4.3)
Hypomagnesaemia	02 (1.7)
4. Structural brain injuries	10(08.6)
Hydrocephalus	06(5.2)
Brain Abscess	02 (1.7)
Cerebral malformations	02(1.7)

**Table 2:** Types of neonatal seizures.

Type of seizures	Number (%)
1. Generalized tonic	28 (24.1)
2. Focal clonic	30 (25.9)
3. Multifocal clonic	22 (19.0)
4. Myoclonic	10(8.6)
5. Subtle	26(22.4)
5.1.Ocular phenomena	10 (38.5)
5.2.Oral phenomena	10 (38.5)
5.3.Autonomic phenomena	03 (11.5 )
5.4.Fragmentary body movements	03 (11.5)
Total	116(100.0)

**Table 3:** Relation between seizure type and underlying cause.

Type of seizures	Underlying Causes				p- value
	Hypoxic-ischemic encephalopathy	CNS or systemic infections (Meningitis/septicemia)	Primary Metabolic causes	Structural brain injuries	
1. Generalized tonic	20(71.4)	05(17.9)	02(7.1)	01(3.6)	0.01
2. Focal clonic	13(43.3)	06(20.0)	08(26.7)	03(10.0)	0.06
3. Multifocal clonic	12(54.6)	06(27.3)	02(9.0)	2(9.0)	0.1
4. Myoclonic	02(20.0)	2(20.0)	3(30.0)	3(30.0)	0.23
5. Subtle	01 (03.9)	7(26.9)	17(65.3)	1(03.9)	0.001
Total	48(41.4)	26 (22.4)	32(27.6)	10(08.6)	116(100.0)

respectively. Neonates with biochemical abnormalities (Hypoglycemia, Hypocalcaemia, Hypomagnesaemia and Hyponatremia) had better seizure control than those with hypoxic-ischemic encephalopathy and meningitis or septicemia. Mode of delivery had no significant effect on seizures control (p-value = 0.1).

## DISCUSSION

One hundred and sixteen neonates were enrolled in this study. However we were only able to document seizures that were clinically evident. It is possible that we missed subclinical seizures, given the fact that electro-clinical dissociation is more common in neonates than in other age groups [7]. The electroencephalograph monitoring could have led to more accurate estimation of the burden of seizures in this age group. Nicholas S mentioned that about 80–90% of electrographic seizures do not have any associated clinical symptoms and would not be identified without continuous EEG. Further complicating the matter, anticonvulsant administration may terminate clinically evident seizures while electrographic-only seizures persist [8].

In this study 116(7.7%) neonates had seizures as a major presenting symptom. Bonifacio SL et al stated that seizures are one of the most common neurologic problems managed by neonatal neurocritical care services, occurring in 1–5 per 1000 live births [9].

We report that 27 (23.3%) mothers had medical problems related to pregnancy; most common are diabetes, hypertension and infection. This is similarly reported by Hall DA et al that infection and preexisting diabetes in the mother were risk factors for neonatal seizures in term infants and these findings are confirmatory of previous reports that maternal preexisting diabetes increases the risk of neonatal seizure in term infants [10]. The majority of neonates who developed seizures were delivered at term (7.2% as compared to 3.1% in preterm group), however it is reported that neonatal seizures affect up to 1.5–3.5/1000 full-term newborns and 10–130/1000 preterm infants [11]. Carlotta Spagnoli et al reported that the prevalence of seizures in preterm newborns is higher than in full-term ones (22.2% compared to 0.5%). The seizure outcome was better in term newborns as opposed to preterm ones (p- value =0.001), which was similarly reported in the literature [12–15].

The most common cause of seizures in this study was neonatal encephalopathy and infections. Both conditions are preventable and, using simple public health interventions, it

should be possible to reduce the burden of neonatal seizures and hence brain injury in our population. Broad measures, such as ensuring safe deliveries, appropriate neonatal resuscitation and early treatment of infections in the neonatal period, may have the effect on reduction of seizures burden. Denish S. et al reported that birth asphyxia was the most common cause of neonatal seizures and account for 64.5%, followed by neonatal meningitis 24.2% and Islam MN, et al reported (78%) of neonates to have HIE followed by Septicemia [16,17].

Primary Metabolic causes were detected in 32(27.6%) with hypocalcaemia being the commonest which is similarly reported by Anjali Kher et al [18].

We found that 51.7% of the neonates had first attack of seizures within the first 24 hours of life, higher rate were reported from India and Iran [19,20]. The most common type of seizures was focal clonic 25.1% followed by GTC in 24.1%, Shahzad Najeeb et al from Pakistan reported tonic clonic seizure was the commonest type (28%) followed by multi-focal clonic, and focal tonic seizures (25%) each [21]. Subtle seizures were reported in 19.8% this was similarly reported by Islam MN et al [17] and Denish S. et al. [16].

This study reported that (77.6%) neonates received one AED drug, the commonest is Phenbarbitone followed by Levetiracetam, though Jensen FE agreed that Phenbarbitone is often ineffective as a first line anticonvulsant in neonates with seizures in whom the background EEG is significantly abnormal and this may reflect the importance of EEG in neonatal seizures [22]. In South Korea, Han JY et al stated that in the recent decades, Levetiracetam has been increasingly used for the treatment of neonatal seizures [23]. We report that 76.7% of the neonatal seizures were well controlled and no deaths, this may be due to short term follow up and further research are needed to look for the possible long term sequelae of seizures in the neonatal period.

## CONCLUSION

The most common cause of neonatal seizures in our set up are hypoxic ischemic encephalopathy followed by neonatal sepsis/ meningitis, however seizures outcome is good. Neonates whose mothers had illnesses related to pregnancy, neonates with generalized seizures, preterm delivery, seizures started in the first 24 hours of life and neonates with abnormal brain image, had poorly controlled seizures.

Facilities for Neonatal resuscitation, prevention of Birth Asphyxia and safe deliveries are mandatory at all levels of

health care systems. The medical and paramedical staff should be trained in anticipating, monitoring and observation for subtle seizures and treatment protocols of neonatal seizures. EEG service and metabolic screening are of paramount and need to be available in our setup.

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