A clinical study on biochemical profile of neonatal seizures in a medical college hospital

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Abstract---Background: Neonatal seizures are one of the most common and distinctive clinical manifestations of dysfunction of neurological system. Neonatal seizures represent non-specific responses of the immature nervous system to varied insults and result in considerable neonatal mortality and long- term morbidity including motor and cognitive disabilities in the childhood. OBJECTIVES: To study the biochemical abnormalities associated with neonatal seizures. To study the clinical presentation, time of onset and its relation to the neonatal seizures in new-born unit. Material & Methods: Study Design: Prospective hospital based observational study. Study area: Dept. of. Paediatrics, Mamata Academy of Medical Sciences, Bachupally, Hyderabad, Telangana. Study Period: June 2021 – May 2022. Study population: All the neonates from birth to 28 days of life satisfying the inclusion and exclusion criteria who got admitted in the Neonatal Intensive Care Unit of Department of Pediatrics. Sample size: study consisted a total of 80 cases. Study tools and Data collection procedure: Written informed consent was taken from the parent or caregivers prior to the enrolment of neonate for the study. Detailed antenatal history like, maternal age, past medical history, parity, gestational age, history of illness during pregnancy, medication during pregnancy, natal history like, evidence of fetal distress, Apgar score, type of delivery, and medication given to mother during delivery and perinatal history were recorded. Results: The mean ± SD birth weight of study population was 2.56 ± 0.67 with minimum 0.99 kg and maximum 4.16 kg. Among the study population, babies with Low birth weight (<2.5kg) were 35 (43.75%), and with Normal Birth weight (≥2.5kg) were 45 (56.25%). The mean day of onset of seizures was 3.26 with minimum 1 and maximum 14 in the study population. Conclusion: Hence biochemical work up

should be done in all neonates with seizures and should be included as the first line of investigations in all cases. Early correction of these biochemical abnormalities help in preventing the further occurrence of seizures and also helps in avoiding over use of anticonvulsants which may be unnecessary in some cases.

Introduction

Neonatal seizures are one of the most common and distinctive clinical manifestations of dysfunction of neurological system. Neonatal seizures represent non-specific responses of the immature nervous system to varied insults and result in considerable neonatal mortality and long- term morbidity including motor and cognitive disabilities in the childhood [1,2]. Although prompt diagnostic and therapeutic interventions are needed, multiple challenges impede the physician's evaluation and management of the newborn with suspected seizures. These neonatal seizures are often under-recognized, and difficult to treat. Hence it is critical to recognize seizures early and initiate immediate therapy. Recognition of etiology is often helpful in prognosis and treatment. Studies suggest that neonatal seizures and their etiology have a significant impact on the developing brain; however, in clinical practice at neonatal intensive care units (ICU), in developing countries where synchronized video-EEG monitoring is practically non-existent, clinical observation becomes the key to the diagnosis [3].

Biochemical abnormalities are one of the most common causes of neonatal seizures which may be primary or associated with other causes for which specific treatment is available. Early identification and correction of these biochemical disturbances are necessary to control seizures and to prevent permanent brain damage, as antiepileptic drugs alone are generally ineffective if the electrolyte disorder persists. The prognosis and the outcome of the neonates also depends upon the etiology of seizures. Since seizures due to transient metabolic disturbances if identified and treated early, it is associated with good prognosis and further we can prevent long term sequelae like cognitive deficits ranging from learning disability to developmental delay, cerebral palsy and mental retardation, as well as later life epilepsy as reported by various studies. To avoid the unwanted long term use of anticonvulsants and to prevent the side effects associated with their use. Hence we undertook the study in neonatal unit to find out the biochemical abnormalities associated with neonatal seizures.

Objectives

- To study the biochemical abnormalities associated with neonatal seizures.
- To study the clinical presentation, time of onset and its relation to the neonatal seizures in new-born unit.

Material and Methods

Study Design

Prospective hospital based observational study.

Study area

Dept. of. Paediatrics, Mamata Academy of Medical Sciences, Bachupally, Hyderabad, Telangana

Study Period

June 2021 - May 2022.

Study population

All the neonates from birth to 28 days of life satisfying the inclusion and exclusion criteria who got admitted in the Neonatal Intensive Care Unit of Department of Pediatrics.

Sample size

Study consisted a total of 80 cases. Sample size was determined based on "A Study on Clinico- Biochemical Profile of Neonatal Seizure" authored by Dinesh Das et al published in J Neurol Res. 2016;6(5-6):95-101. In this study, the most common biochemical abnormality detected in neonatal seizures in our study was hyponatremia (26, 65%).

- The confidence level is estimated at 95%
- With a z value of 1.96
- The confidence interval or margin of error is estimated at +/-12
- Assuming p% =65 and q%=35 n = p% x q% x [z/e%] ^{2}

n= 65x 35 x [1.96/12]^2
n= 60.69 (rounded to 61)
With Attrition 10% = 61+6=67

Therefore 67 is the minimum sample size required for the study assuming 80% as the power of study.

Sampling method

Simple Random sampling method.

Inclusion criteria

All Term and preterm babies presenting with seizures including both intramural and extramural neonates were enrolled in the study.

Exclusion criteria

Neonates with the following were excluded from the study, Babies already on anticonvulsant therapy, Mothers or caregivers not giving consent for the study.

Ethical consideration

Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure

Written informed consent was taken from the parent or caregivers prior to the enrolment of neonate for the study. Detailed antenatal history like, maternal age, past medical history, parity, gestational age, history of illness during pregnancy, medication during pregnancy, natal history like, evidence of fetal distress, Apgar score, type of delivery, and medication given to mother during delivery and perinatal history were recorded. Baseline characteristics of all the babies were noted on the prescribed proforma which includes name, age, sex, address weight, length, head circumference, gestational age, which is determined from mother by last menstrual period or ultrasound study of fetus before birth or by new Ballard scoring of the neonate. Thorough physical examination was done and seizures were diagnosed by clinical observation. Clinical details of each seizure episode were recorded like age at onset of seizures, duration of seizure, number and type of seizure. Seizure was classified into subtle, focal clonic, multifocal clonic, tonic, and myoclonic as per criteria by Volpe.

Before instituting specific treatment, 3ml of blood will be collected by sterile technique in a sterile test tube for following investigations like blood glucose, total serum calcium levels, serum sodium and serum magnesium levels apart from capillary blood glucose estimation by glucostrix method. Random blood glucose was done using glucometer and values were confirmed by estimating plasma glucose levels by glucose oxidase method. Serum sodium and potassium estimation done by ion selective method, Serum total calcium by Arsenazo-3 method, Serum magnesium by Calmagite method with the support of Department of Biochemistry.

Criteria for diagnosing various biochemical abnormalities [4,5,6]

- Hyponatremia: <135 mEq/l
- Hypernatremia :>145 mEq/l
- Hypoglycaemia :
- <40mg/dl (capillary blood)
- <45 mg/dl (venous blood)
- Hypocalcemia :
- <7mg/dl for preterm neonates
- <8 mg/dl for term neonates
- Hypomagnesemia :   <1.5mg/dl
- Hypermagnesemia :   >2.5mg/dl

- Hypokalemia: <3.5 mg/dl
- Hyperkalemia: >5.5 mg/dl

Statistical Analysis

The data was collected, compiled and compared statistically by frequency distribution and percentage proportion. Quantitative data variables were expressed by using Descriptive statistics (Mean ± SD). Qualitative data variables were expressed by using frequency and Percentage (%). P values of <0.05 were considered statistically significant. Data analysis was performed by using SPSS Version 20. Independent sample t-test/ ANOVA/Paired t- test was used to assess statistical significance. Liner regression analysis was done. Regression coefficient, along with its 95% CI and p values are presented.

Observations and Results

A total of 80 neonates with seizures admitted to the neonatal unit of Department of Paediatrics, among them 38 neonates were delivered by normal vaginal delivery, 38 neonates by caesarean section and 4 by forceps delivery.

Table 1
Gender Distribution in the study population

Gender	Number	Percentage
Male	45	56.25%
Female	35	43.75%

Among the study population, the Male were 45(56.25%) and female were 35 (43.75%). Among the study population, the number of babies born within the institution was 66 (82.5%) and the number referred from outside was 14 (17.5 %). Among the study population, the SGA was 21 (26.25%), AGA and LGA was 56 (70%), and 3 (3.75%) respectively.

Table 2
TERM/PRE TERM/POST TERM Distribution in study population

TERM/PRE TERM/POST TERM	Number	Percentage
Preterm	21	26.25%
Term	59	73.75%
Post term	0	0%

Among the study population, the Preterm were 21 (26.25%) and term were 59 (73.75%) and there were no post term. The mean ± SD birth weight of study population was 2.67 ± 0.67 with minimum 0.95 kg and maximum 4.26 kg. Among the study population, babies with Low birth weight (<2.5kg) were 35 (43.75%), and with Normal Birth weight (≥2.5kg) were 45 (56.25%). The mean day of onset of seizures was 3.8 with minimum 1 and maximum 14 in the study population.

Table 3

Descriptive analysis of Day of Onset Category in study population

Day of onset category	Number	Percentage
Within 24 hours	22	27.5%
24 to 72 Hours (day 1 to 3)	35	43.75%
4th day to 1 week (day 4 to 7)	16	20%
More than 1 week (More than 7 days)	7	8.75%

In our study onset of seizures within 24 hours was 22 (27.5%), 24 to 72 Hours (day 1 to 3), 4th day to 1 week (day 4 to 7), and More than 1 week (More than 7 days) was 35(43.75%), 16 (20.00%) and 7(8.75%) respectively. Convulsions in the first 3 days contributes to 71.25%. Among the study population, number of neonates with subtle seizures were 49 (61.25%), Tonic and Clonic were 20 (25%) and 11 (13.75%) respectively.

Table 4

Summary of various biochemical abnormalities in study population

Various Biochemical Abnormalities	Number N=80	Percentage
HYPO GLYCEMIA	19	23.75%
HYPOCALCEMIA	16	20%
HYPO NATREMIA	7	8.75%
HYPO MAGNESIMIA	4	5%
HYPERNATREMIA	4	5%

(Note: The total percentages may not match 100% as this table reported the frequency of various metabolic abnormality which are not mutually exclusive.)

Table 5

Association of TERM/PRE TERM with HYPO GLYCEMIA of study population

HYPOGLYCEMIA	TERM/PRETERM		Chi square	P-value
	Preterm (N=21)	Term (N=59)		
Yes	8 (38.1%)	12(20.3%)		
No	13 (61.9%)	47 (79.66%)	2.236	0.135

Among 21 preterm babies 8 (38.1%) had hypoglycemia, among 59 term babies only 12(20.3%) had hypoglycemia. The difference in proportion of hypoglycemia between term and preterm babies was statistically not significant (P value 0.135).

Table 6

Association of TERM/PRE TERM with Hypocalcaemia of studypopulation

HYPOCALCEMIA	TERM/PRETERM		Chi square	P-value
	Pre term (N=21)	Term (N=59)		
Yes	7 (33.33%)	10 (15.69%)	2.185	0.139
NO	14 (66.66%)	49 (83.05%)		

Among 21 preterm babies 7(33.33%) had hypocalcemia, among 59 term babies only 10(16.94%) had hypocalcemia. The difference in proportion of hypocalcemia between term and preterm babies was statistically not significant (P value 0.139).

Table 7

Association of TERM/PRE TERM with HYPO NATREMIA of study population

HYPO NATREMIA	TERM/PRE TERM		Chi square	P-value
	Pre term(N=21)	Term (N=59)		
Yes	3 (14.28%)	5 (8.47%)		
No	18 (85.71%)	54 (91.53%)	0.127	0.721

Among 21 preterm babies 3 (14.28%) had hyponatremia, among 59 term babies only 5 (8.47%) had hyponatremia. The difference in proportion of hyponatremia between term and preterm babies was statistically not significant (P value 0.721).

Table 8

Association of Term/Pre Term with Type of Seizures of study population

TYPE OF SEIZURES	TERM/PRE-TERM/POSTTERM		Chi square	P-value
	Pre term (N=21)	Term (N=59)		
subtle	13 (61.9%)	36 (61.01%)		
tonic	5(23.8%)	16 (27.1%)		
Clonic	3 (14.28%)	7 (11.8%)	0.407	0.816

Among 21 preterm babies, 13 (61.9%) had subtle seizures,5(23.8%) had tonic, and 3 (14.28%) had clonic type of seizures. Among 59 term babies, 36(61.01%) had subtle, 16 (27.1%) had tonic, and 7 (11.8%) had clonic seizures. The difference in proportion of type of seizures between term and preterm babies was statistically not significant (P value 0.116).

Discussion

Seizures are most common neurological disorders in newborn which are more prevalent in preterm neonates compared to term neonates. In our study, a total of 80 neonates with seizures who got admitted into the neonatal intensive care unit. Out of 80 neonates, full term neonates were 59 (73.75 %) and preterm constitutes 21 in number (26.25%). there were no post term babies in our study. Among 80 neonates, 56 were appropriate for gestational age, 21 were small for gestational age, 3 were large for gestational age constituting about 70%, 26.25%, 3.75% respectively. Majority of neonates with seizures in our study were full term appropriate for gestational age neonates. Similar observations were seen in study by Aziz et al [7] where term babies constitute 65% and preterm 35% and AGA 68%, SGA 26% and LGA 6%. In studies by Park Weon et al [8] and Dinesh Das et al [9], they also reported a much higher incidence in term babies compared to preterm neonates. Dinesh das et al [9] observed seizures in 91.3% of term, 7.8% in preterm and 0.9 % in posterm.

In our study neonatal seizures were common in male babies contributing about 56.25% and female neonates contributes about 43.75%, with a male: female ratio of about 1.28:1. Studies by Aziz et al [7] (male 60%, female 40%) and Dinesh Das et al [9] (male 62.6%, female 37.4%) also reported male predominance. In yet another study by Tekgul et al [10] showed male: female ratio to be 1.15:1 whereas Sudia et al [11] reported 1.73:1further supporting my study that seizures are common in males. In our study, 38 babies (47.5%) born by normal vaginal delivery, 38 babies (47.5%) by caesarian section and 4 babies by forceps delivery (5%). Aziz et al [7] in his study reported neonates with seizures born by normal vaginal delivery in 48%, by lower segment caeserian section in 28% and operated vaginal in 24%. In our study 45 neonates (56.25%) had birth weight >2.5kg and 35 neonates (43.75%) had birth weight < 2.5 kg. similar observations were made by Dinesh Das et al [9] where neonates >2.5 kg were 65% and <2.5kg were 35% respectively.

In our study out of 80 neonates, 22 had seizures within 24 hours (27.5%), 35 neonates between 24-72 hours (43.75%), 16 babies between day 4 to 7 (20%) and 7 babies above 7 days (8.75%). Thus most of the seizures occurred within the first 3 days of life contributing about 71.25% of neonates in our study. Similar observations were made by Dinesh Das et al [9] where seizures within 3 days was reported to be 71.3% and Nawab et al [12] observed 73.6 % of neonatal seizures within 3 days which were comparable with our study. We found in our study that subtle seizures were the most common type of neonatal seizures contributing to about 61.9% in about 49 neonates, followed by tonic seizures in 26.25% and clonic seizures in about 12.5% of neonates. Similar findings were reported by Sudia et al [11] where subtle seizures occurred in 63.33% followed by generalized tonic in 19.33% and multifocal clonic in 10% of neonates. Dinesh das et al [9] in his studies on neonatal seizures also observed subtle seizures to be the commonest type contributing about 42.6% followed by tonic in 33.9% and clonic in 15.7% of neonates. Various studies by Yadav et al [13], Park Weon et al [8] and Nawab et al [12] also reported subtle seizures to be the most common type observed in their studies which were comparable with our study.

In our study, out of 80 neonates, 50 babies with seizures had one or more biochemical abnormalities contributing to about 62.5% in total. Sood et al [14] in his study has observed overall biochemical abnormalities in 29 cases constituting of about 49.15 % which was comparable with our study. Similar observations were made by Nawab et al [12] in his studies where out of 110 neonates, 46 babies had biochemical abnormalities contributing about 41.8% cases in total. Kumar et al [15] has found overall biochemical abnormalities in 62.8% of neonates against Madhusudan et al's [16] 43.33%.

The most common biochemical abnormality reported in our study were hypoglycemia followed hypocalcaemia particularly in preterm neonates. Among preterm babies the incidence of hypoglycemia was 38.1% compared to 20.3% in term babies. Hypocalcaemia was reported in 33.33% among preterm babies which was higher when compared with term babies of about 16.94%. Suganthi et al [77] in her study has made similar observations where Metabolic abnormalities were present in 89(59.3%) out of 150 cases. Of these, hypoglycemia and hypocalcemia were the most common with 39 (43.8%) and 28 (35.4%) cases respectively. In our study 4 cases had been reported with combination of hypoglycemia and hypocalcemia (5.%) and 2 cases with hypocalcaemia and hypomagnesaemia (2.5%) in our study occurring especially in preterm neonates. Sudia et al [18] in her study had reported hypoglycemia and hypocalcemia combination in 9% and hypocalcemia hypomagnesemia combination in 7.9% cases. Nawab et al [12] also described occurance of similar combinations in his study.

Conclusion

Hence biochemical work up should be done in all neonates with seizures and should be included as the first line of investigations in all cases. Early correction of these biochemical abnormalities help in preventing the further occurrence of seizures and also helps in avoiding over use of anticonvulsants which may be unnecessary in some cases. Further early correction of these metabolic disturbances improve the prognosis and outcome of the neonate and also prevent the long term neurological sequelae associated with it.

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