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Serum calcium level in neonatal seizures presenting at a Tertiary Care Hospital.

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ABSTRACT... Objectives: The present study was conducted to detect serum calcium level in neonatal seizures presenting at a Tertiary Care Hospital. **Study Design:** Case control study. **Setting:** Department of Paediatrics, Shaheed Muhtrama Benazir Bhutto Medical. College Layari General Hospital, Karachi, Sindh. **Period:** June 2017 to January 2018. **Material & Methods:** The sample comprised of 100 cases and 100 controls that were selected through non-probability purposive sampling through inclusion and exclusion criteria. Sera were separated through centrifugation of blood for measuring the serum calcium levels. Data was analyzed on SPSS software (SPSS ver 22.0, IBM, Incorporation, USA) at 95% confidence interval ($P \leq 0.05$). **Results:** Of 100 cases and 100 controls, the male and female were noted as 61 vs. 57 and 39 vs. 43 respectively ($P > 0.05$). In cases, the mean \pm SD Ca^{++} was noted as 4.17 ± 1.58 mg/dl while in control it was noted as 8.15 ± 1.05 mg/dl. Ca^{++} levels as low as 3.07 mg/dl were noted in the neonatal seizure cases. Normocalcaemia was noted in 81 controls vs. 11 cases and hypocalcaemia in 18 controls vs. 89 cases. **Conclusion:** The present study reports hypocalcaemia is common in neonatal seizures. Pediatricians must evaluate for timely correction of serum calcium to prevent long term neurological sequelies.

Key words: Neonates, Neonatal Seizures, Serum Calcium, Sindh.

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INTRODUCTION

Seizure is one of commonest neurological manifestation of biochemical disturbance in neonates presenting in emergency room. Seizures occur because of a numbers of causes. Neonates are at particular risk of seizures because of metabolic, infectious, toxic and congenital disorders.¹ Manifestation of neonatal seizure is extremely subtle.^{1,2} Neonatal seizure presenting with multiple signs such as lip smacking, cycling movements, eye blinking, eye deviation, nystagmus, and respiratory rate problem such as apnea may the presenting manifestations that are sometimes difficult to discriminate from normal neonatal movement.^{1,3} A 20% prevalence of seizure has been reported in neonates in intensive care unit.^{4,5} However, neonatal seizure prevalence ranges from as low as 0.5% in full term

babies to as high as 21% in preterm (premature) babies.^{6,7} Seizure is not a diagnosis but a sign of an underlying abnormality that may be systemic or biochemical in nature.⁷ Biochemical disturbance of electrolytes are frequent in the neonatal seizure. Sometimes it is difficult to control and further neuronal damage may occur if treatment is delayed. Early recognition and prompt correction of biochemical disturbances is necessary for the satisfactory long term outcome.⁵ Biochemical disturbances of clinical significance that predispose to seizures include the; electrolyte imbalance and hyperbilirubinemia, etc. Electrolyte disorders include the hyponatremia and hypernatremia, hypokalemia and hyperkalemia, hypomagnesaemia, hypoglycemia, hypocalcaemia and hypercalcemia.^{7,8} Of these biochemical abnormalities, the hypocalcaemia

is by far the most common in inducing neonatal seizure. Hypocalcaemia is the most common cause of neonatal seizure followed by hypoglycemia and hypomagnesaemia.⁵ Hypocalcaemia may manifest clinically as neuronal hyper-excitability and seizure, neuromuscular excitability called tetany and delirium. Spontaneous neuronal excitability is rule with hypocalcaemia and a common predisposing factor of brain seizures.^{9,10} Hypocalcaemia is defined as serum Ca^{++} levels $<7\text{mg/dl}$.⁷ Various mechanisms have been proposed by which the hypocalcaemia predisposes to seizure through neuromuscular excitation. One proposed mechanism is spontaneous neuronal depolarization caused by spontaneous Na^+ channels opening of in the presence of hypocalcaemia.^{9,10} Hypocalcaemia induced brain seizure is a serious medical emergency of neonates.¹¹ Keeping in view, the biochemical abnormality of low serum calcium, there is need to further evaluate the gravity of a simple problem evolving in serious clinical condition of brain seizures in newborn. There is dire need to highlight the issue of brain seizure in neonates and readdress its simple management through correction of serum calcium. The present prospective study addresses on the serum calcium levels in neonatal seizures presenting at a tertiary care hospital.

MATERIAL & METHODS

This case control study took place at the Department of Paediatrics, Shaheed Muhtrama Benazir Bhutto Medical College Layari General Hospital, Karachi, Sindh from June 2017 to January 2018. Neonates were selected according to inclusion and exclusion criteria presenting at the Department of Pediatrics of our tertiary care hospital. Pediatric Department is fully equipped with a neonatal intensive care unit. All facilities are available therein. 200 neonates were recruited through non-probability convenient sampling according to inclusion and exclusion criteria.

Neonates were divided into cases ($n=100$). Inclusion criteria for cases were defined as those babies presenting with seizures with apparently no detectable problem, had no history of fever, septicemia, birth asphyxia and injuries and no

other obvious cause of convulsion detected. Another 100 neonates ($n=100$) were labeled as control. Inclusion criteria for control were; those babies presenting with seizures with detectable problem such as fever, septicemia, meningitis, and any other illness who were admitted to neonatal ICU without any convulsion. Informed consent was taken from the parents/guardians. Study protocol was approved by the institutional ethical committee according to the Helsinki's declaration for conducting human research. History was taken from the parents/attendants/guardians about presenting illness. Peri-natal history, family history of epilepsy, past seizures, economic status was noted. Neonates were examined physically. Authors designed a proforma for data to be noted in it. Serum Ca^{++} level $<7\text{ mg/dl}$ (1.75 mmol/L) was defined as hypocalcemia.⁷ Neonatal seizures were treated by diazepam (0.5 mg/kg) parenteral/per rectal. Once seizures were over, venesection was performed. 2 ml blood was taken from peripheral vein. Sera were separated from blood by centrifuging at 3000 rpm (10 minutes). Serum calcium was estimated by "Colorimetric method".¹² Colorimetric method is based on the serum Ca^{++} measurement by chelating with EDTA in the presence of "murexide indicator". Readings were noted at filter peak of 5750-5800 A on an EEL photoelectric titrator. Confidentiality of data was maintained. Ethical permission was taken from institute and consent form was signed by parents/guardians. Data was typed on Microsoft Excel sheet. This was copied and pasted on SPSS sheet (SPSS ver 22.0 for windows, IBM, Incorporation, USA) and analysis was performed. Cross tabulation was applied for Chi square for the categorical data. Results were presented as frequency and %. Independent samples Student's t-tests was applied to continuous variables and results were presented as mean and standard deviation (SD). Confidence interval of significance was taken at 95% ($P \leq 0.05$).

RESULTS

Age (mean \pm SD) in cases and controls was 3.2 ± 0.5 days and 3.1 ± 0.03 days respectively ($P > 0.05$). Seizure frequency is shown in Table-I. 94 controls showed convulsion frequency of <1

while 84 cases showed ≥ 4 convulsions (Table-I) ($p=0.0001$). Nature of convulsions was; focal in 37%, subtle in 31% and mixed in 32% of cases (Figure-1). Duration of convulsions is shown in Table-II. Duration of <5 minutes seizures in controls were noted in 7 and in cases in 73. In cases, 27 babies showed duration of 5- 30 minutes. Of 100 cases and 100 controls, the male and female were noted as 61 vs. 57 and 39 vs. 43 respectively (Figure-2) ($P > 0.05$). Table-III (Figure-3) shows the calcium distribution of control and cases. In cases, the mean \pm SD Ca^{++} was noted 4.17 ± 1.58 mg/dl while in control it was noted as 8.15 ± 1.05 mg/dl. Ca^{++} levels as low as 3.07 mg/dl were noted in the neonatal seizure cases. Normocalcaemia was noted in 81 controls vs. 11 cases and hypocalcaemia in 18 controls vs. 89 cases as shown in Table-IV (Figure-4).

Frequency	Control	Cases	P-Value
0	51	0	0.00001
≤ 1	43	3	
2	6	2	
3	0	11	
4	0	31	
≥ 5	0	53	
Total	100	100	

Table-I. Frequency of neonatal seizure in control and cases

Nature of seizure in cases

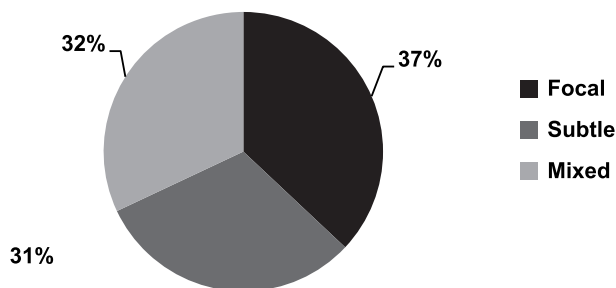


Figure-1. Nature of seizures in cases

Duration	Control	Cases	P-Value
<5 minutes	7	73	0.0001
5- 30 minutes	0	27	

Table-II. Duration of seizures in control and cases

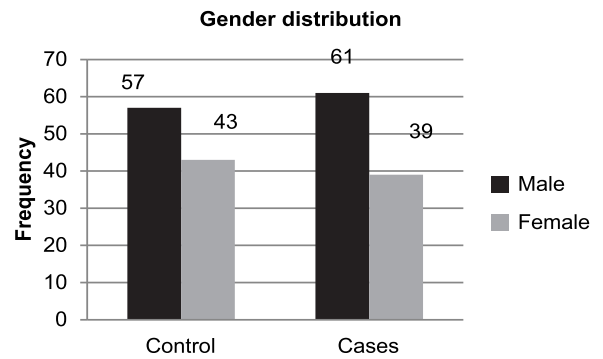


Figure-2. Bar graph showing gender distribution

Serum Ca^{++} (mg/dl)	Control	Cases	P-Value
≤ 3.9	1	13	0.00001
4 - 4.9	1	25	
5 - 5.9	3	21	
6 - 6.9	13	30	
7- 7.9	31	7	
≥ 8.0	51	4	
Total	100	100	

Table-III. Serum calcium levels in in control and cases

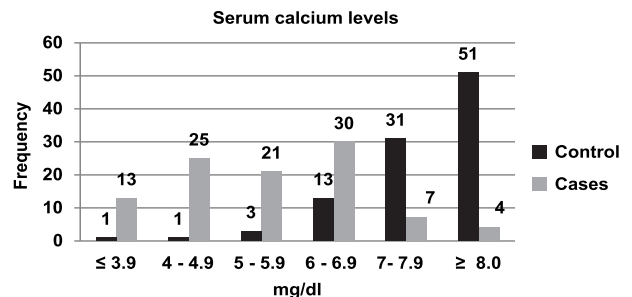


Figure-3. Bar graph showing frequency of calcium levels

	Control	Cases	P-Value
Hypocalcaemia	11	93	0.00001
Normocalcaemia	89	7	
Total	100	100	

Table-III. Hypocalcaemia and Normocalcaemia in control and cases

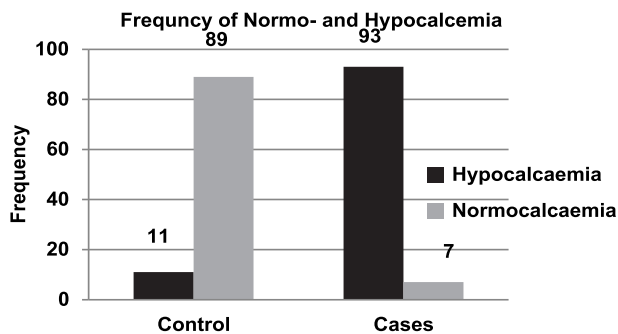


Figure-4. Bar graph showing frequency of Normo- and hypocalcaemia

DISCUSSION

A search of literature shows, this is the first study being reported from out tertiary care hospital on the serum calcium levels in neonatal seizures presenting with afebrile fits. The cases were compared with age and gender matched controls and those suffering from neonatal seizures were having no apparent cause of convulsion. Of 100 cases and 100 controls, the male and female were noted as 61 vs. 57 and 39 vs. 43 respectively ($P > 0.05$). This is consistent to previous studies.³⁻⁸ In present study, the hypocalcemia was noted in 89% of cases of neonatal seizures compared to 11% in controls. While 81% of controls showed normocalcemia compared to 11% neonatal seizure cases (Table-IV). Our finding of 89% hypocalcemia in neonatal seizures is consistent with previous studies.³⁻⁸ Consensus is lacking on the cut off value of serum calcium level as hypocalcemia.

Literature does not show evidence of exact serum calcium levels that defines neonatal hypocalcemia.^{7,8} Various cut off values are defined such as serum $Ca^{++} < 8$ mg/dl⁸, < 7.5 mg/dl and < 7 mg/dl.^{6,7} Baten et al¹³ conducted a study on serum calcium levels in neonatal seizures with 50 cases and reported hypocalcemia in 60% of cases. The finding is in agreement with present however, less percentage of above study¹³ may be due to small sample size. Cockburn et al⁸ conducted a longitudinal study of 2 years duration on neonatal convulsions. They reported primary defect of mineral metabolism in 55% of neonatal convulsions. The findings of present study are more prevalent found in 89% hypocalcemia in

neonatal seizures. This may be due to the fact that the vitamin D deficiency is prevalent in the country^{14,15} and there is no data in this regard on the neonatal seizures. The mothers lacking vitamin D may give birth to hypocalcemia neonates. Another study by Kumar et al¹⁶ reported primary metabolic disorder in 25% of cases of neonatal seizures. This frequency is very small and is inconsistent with present and previous studies.^{8,13} Approximately, 94 controls showed convulsion frequency of < 1 while 84 cases showed ≥ 4 convulsions ($p=0.0001$). Nature of convulsions was; focal in 37%, subtle in 31% and mixed in 32% of cases. The findings are supported by previous studies.^{8,14} In developing countries, the metabolic cause of neonatal seizure is due to malnourished mothers, infrequent breast feeding, delayed breast feeding and faulty feeding practices. This is in contrast to studies from western countries¹⁶, where breast feeding practices have made this problem very uncommon.

A previous study⁶ reported the hypocalcemia is very common in neonates in developing countries mainly due to primary metabolic abnormalities. Similar findings have been reported from western countries.¹⁶ Sood et al⁵ reported from India that the hypoglycemia is common cause of neonatal followed by hypocalcaemia. This is in contrast to present and previous studies.^{6,8,13} In present study, 11% of controls were suffering from hypocalcemia that is comparable to the Baten et al¹³ that noted in 20% of control. In present study, the duration of < 5 minutes seizures in controls were noted in 7 and in cases in 73. In cases, 27 babies showed duration of 5- 30 minutes. The findings are in agreement with previous studies.^{7,13} Duration of neonatal seizure of > 30 minutes indicates poor prognosis.^{7,13} In present study majority of cases were having duration of seizure of < 5 minutes that is consistent with a previous study.¹³ In present study, mean \pm SD Ca^{++} was noted 4.17 ± 1.58 mg/dl in cases while in control it was noted as 8.15 ± 1.05 mg/dl. Ca^{++} levels as low as 3.07 mg/dl were noted in the neonatal seizure cases. The findings are in agreement with previous studies.^{13,17-19} Baten et al¹³ reported mean serum Ca^{++} level of $1.62 \pm .29$ in cases that was less than in controls $2.07 \pm .30$ mmol/L and

difference was statistically significant ($p < 0.0001$). Another previous study¹⁷ conducted with cases of neonatal seizure, reported high incidence of hypocalcaemia in full term and premature infants. Similar is another previous study¹⁸ high incidence of hypocalcemia induced convulsion. Above studies^{13,17,18} are in support with the findings of our present study. A recent study¹⁹ reported high incidence of hypocalcemia in neonatal seizures admitted in level III neonatal intensive care units. Recent studies by Elsary et al²⁰ and Do HJ et al²¹ have reported neonatal hypocalcemia and neonatal seizures and support the findings of present study. The limitations of present study include; first- small sample size, second- poor ethnical group of sample population was selected, third- other variables were not measured due to financial issues. However, the strength of study lies in its prospective study design and inclusion criteria. The findings of present are worth to report and will add much to the literature on the topic of neonatal seizures and hypocalcemia. Large sample size studies are recommended to be conducted in the future along with associated factors like race, ethnicity and geography.

CONCLUSION

The present study reports hypocalcemia is very common metabolic defect in neonatal seizures, where other cause is not identified. Early recognition and prompt correction of serum calcium may prevent against the long term neurological sequelies. Clinical practitioners should be aware of a common modifiable defect of hypocalcemia. Further large scale studies are warranted to dig into the gravity of the problem and this will help making national guidelines for neonatal seizures.

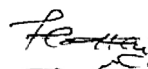
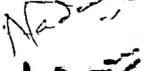

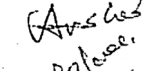
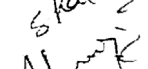
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2	Nadeem Noor	Material handling, Interpretation, Proof reading.	
3	Adnan Bashir	Concepts initial handling, Collection of materials, Compilation result, manuscript.	
4	Bilawal Hingorjo	Literature review, concept, material handling, proof reading.	
5	Arshad Ali	Concepts materials handle, interpretation, manuscript write up.	
6	Urooj Tabassum	Concept, materials handle, Collection of materials, Compilation of results.	