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Original research article

A Case Control Study to Assess the Serum Vitamin D Levels in Neonates with and without Seizures

Dr. Pradeep Sharan[1], Dr. Jai Prakash Narayan[2]

[1]Senior Resident, Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India

[2]Associate Professor, Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India

Corresponding Author: Dr. Jai Prakash Narayan

Abstract

Aim: To evaluate the Vitamin D Levels in Neonates With and Without Seizures.

Methods: A case control study was conducted in the Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India from May 2019 to April 2021. Term and late preterm (35-40 weeks) neonates admitted to the neonatal intensive care unit (NICU) of our institute with seizures were enrolled as cases. Controls were healthy term and late preterm neonates admitted in the postnatal ward along with their mothers. Blood samples of all neonates with seizures included in the study were sent for vitamin D levels, calcium, and magnesium along with other investigations like sepsis screen (to rule out septicemia), ammonia, lactate, pyruvate, ABG, TMS/GCMS (to rule out IEM), blood glucose, ionized calcium and total calcium, and serum albumin. Blood samples were taken immediately after seizures and before administration of any specific treatment. Second-line investigations were done in cases, as and when indicated. These included electro- encephalography (EEG), cerebrospinal fluid analysis, and neurosonogram/magnetic resonance imaging. Serum vitamin D estimation was done by electro-chemiluminescence immunoassay.

Results: total of 100 babies with seizures were admitted to the NICU during the study period, of which 50 were excluded. 50 neonates were enrolled as controls. Baseline characteristics of cases and controls were not significantly different . Based on the semiology, the most common seizures were multifocal clonic type (n=15), followed by focal clonic (n=13). Mixed type and subtle seizures were seen in six neonates each, and tonic and myoclonic types in one each. Based on the etiology, idiopathic seizures were the most common (n=40) followed by hypocalcemic seizures (n=8). The serum vitamin D levels were higher in cases than the controls (P=0.22); although, both groups had levels in the insufficient range (15-20 ng/mL) . There were 30 neonates with seizures with low vitamin D levels (<20 ng/mL). Out of which, 10 mothers' samples could not be done as they were not willing and/or were not admitted to the same Institute as the babies were outborn. The mean (SD) serum vitamin D levels of remaining mothers (n=20) was 14.25 (5.17) ng/mL and the mean serum vitamin D levels of their babies (n=20) was 14.04 (3.55) ng/mL. There was no significant association (P=0.71) between maternal and neonatal vitamin D levels. There was no significant association (P=0.22) between onset of seizures (within and beyond 72 hours) and vitamin D levels. Levels of vitamin D were low among neonates with hypocalcemic seizures but it was not statistically significant [16.02 (7.79) vs 21.02 (5.88); P=0.17]. Among the cases, EEG was done in 40 babies. Out of the 40 EEGs, only three were abnormal.

Conclusion: Hypovitaminosis D in mothers is also associated with hypovitaminosis D in neonates.
Keywords: vitamin D, neonates, seizures

Introduction

Apart from being the cardinal manifestation of epilepsy, seizures can be the result of numerous transient conditions that cause neuronal excitation, such as fever, electrolyte disturbances, central nervous system infections such as meningitis or encephalitis, bleeding, ischemia, or head trauma.[1] Hypocalcemia in a term infant is defined as a total serum calcium <8 mg/dL or an ionized calcium <4.4 mg/dL. Late- onset hypocalcemia is defined as hypocalcemia that occurs in neonates after the second or third day of life. Most infants with hypocalcemia are asymptomatic; those who present with symptoms most commonly present with increased neuro- muscular irritability or seizures[2] and less commonly with stridor, wheezing, or vomiting caused by laryngospasm, bronchospasm, or pylorospasm, respectively.[3] The majority of infants with hypocalcemia have parathyroid hormone (PTH) insufficiency, low vitamin D (25-hydroxy vitamin D), low magnesium, or are formula fed.[4] Treatment of symptomatic hypocalcemia in infants begins with administration of intravenous (IV) calcium gluconate followed by oral calcium for maintenance therapy and identification and treatment of contributing factors such as hypomagnesemia, hyperphosphatemia, and vitamin D deficiency (VDD).[5]

Material and Methods

A case control study was conducted in the Department of Pediatrics, Shri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India from May 2019 to April 2021 , after taking the approval of the protocol review committee and institutional ethics committee.

Term and late preterm (35-40 weeks) neonates admitted to the neonatal intensive care unit (NICU) of our institute with seizures were enrolled as cases. Controls were healthy term and late preterm neonates admitted in the postnatal ward along with their mothers.

Exclusion criteria

Neonates with congenital anomalies, meningitis, hypoglycemia, birth asphyxia, or inborn errors of metabolism; neonates with mothers having hepatic, renal, or bone disorders, mothers on enzyme-inducing drugs and COVID-positive neonates; and neonates with vitamin D supplementation or neonates who were administered antiepileptic drugs before admission.

Blood was drawn for 25-hydroxy vitamin D levels (25(OH)D) from enrolled neonates admitted with seizures. The mothers' vitamin D levels were also evaluated in those neonates with seizures who had vitamin D deficiency. Controls were evaluated for vitamin D levels during day 3-7 investigations like serum bilirubin levels. A detailed antenatal, intranatal and postnatal history was taken in a pre-designed proforma. Whether mothers had received antenatal calcium and vitamin D supplementation and compliance history was also taken. Baseline anthropometry was carried out for all neonates at admission. All babies with seizures who satisfied the inclusion criteria were examined at admission with a detailed examination of the central nervous system. Clinical details of the witnessed seizure episode were noted and details at the time of first seizure and the type of seizure were noted. The neonatal seizures were classified as per Volpe classification into subtle, multifocal tonic, focal clonic, focal tonic, and myoclonic.

Blood samples of all neonates with seizures included in the study were sent for vitamin D levels, calcium, and magnesium along with other investigations like sepsis screen (to rule out septicemia), ammonia, lactate, pyruvate, ABG, TMS/GCMS (to rule out IEM), blood glucose, ionized calcium and total calcium, and serum albumin. Blood samples were taken immediately after seizures and before administration of any specific treatment. Second-line investigations were done in cases, as and when indicated. These included electro- encephalography (EEG), cerebrospinal fluid analysis, and neurosonogram/magnetic resonance imaging. Serum vitamin D estimation was done by electro-chemiluminescence immunoassay.

Serum vitamin D concentrations >20 ng/mL was considered as sufficient, between 12-20 ng/mL as insufficient and <12 ng/mL as deficient.[6] Neonatal hypocalcemia was defined as a total serum calcium concentration of <7 mg/dL or an ionized calcium concentration of <4 mg/dL (1 mmol/L).[7]

Statistical analysis

Statistical analysis was done by using the statistical package for social sciences (SPSS) version 21.0. Comparison of mean values was done by paired and unpaired Student *t*-test and chi-square test. *P* value <0.05 was considered significant.

Results

A total of 100 babies with seizures were admitted to the NICU during the study period, of which 50 were excluded. 50 neonates were enrolled as controls. Baseline characteristics of cases and controls were not significantly different (Table I).

Based on the semiology, the most common seizures were multifocal clonic type (*n*=15), followed by focal clonic (*n*=13). Mixed type and subtle seizures were seen in six neonates each, and tonic and myoclonic types in one each. Based on the etiology, idiopathic seizures were the most common (*n*=40) followed by hypocalcemic seizures (*n*=8).

The serum vitamin D levels were higher in cases than the controls (*P*=0.22); although, both groups had levels in the insufficient range (15-20 ng/mL) (Table I). There were 30 neonates with seizures with low vitamin D levels (<20 ng/mL). Out of which, 10 mothers' samples could not be done as they were not willing and/or were not admitted to the same Institute as the babies were outborn. The mean (SD) serum vitamin D levels of remaining mothers (*n*=20) was 14.25 (5.17) ng/mL and the mean serum vitamin D levels of their babies (*n*=20) was 14.04 (3.55) ng/mL. There was no significant association (*P*=0.71) between maternal and neonatal vitamin D levels.

There was no significant association (*P*=0.22) between onset of seizures (within and beyond 72 hours) and vitamin D levels. Levels of vitamin D were low among neonates with hypocalcemic seizures but it was not statistically significant [16.02 (7.79) vs 21.02 (5.88); P=0.17]. Among the cases, EEG was done in 40 babies. Out of the 40 EEGs, only three were abnormal.

Table I: Baseline Characteristics and Serum Vitamin D Levels in Neonates with Seizures and Controls

Characteristics	Cases (n=50)	Controls (n=50)
Birthweight, g[a]	3123 (567)	2916 (488)
Low birthweight	9(19)	11 (25)
Gestational age, wk[a]	38.93 (1.5)	37.9(1.2)
Male gender	32 (64%)	26(52%)
Late preterm	7(14%)	9 (18%)
Maternal age, y[a]	30.9 (5.1)	29.9 (4.3)
Cesarean section	28 (56%)	31 (72%)
Vitamin D levels, ng/mL[b]	21.02	16.02
	(15.3-22.9)	(13.3-20.9)

Discussion

We found that majority of mother-neonate pairs in this study had low vitamin D levels. Vitamin D levels were low in both cases and controls, with no significant association of low vitamin D level in neonates and occurrence of seizures.

Vitamin D levels were low in controls probably because low birthweight and late preterm babies were more among controls than cases, and mean birth weight was less among controls than cases. Mean vitamin D levels among the mothers whose babies had low vitamin D levels were also low. Possibly mothers in this part of the country have low vitamin D levels as previously also reported [8] , which did not improve even after antenatal vitamin D supplementation. Aparna, et al.[9] also reported that vitamin D deficiency was highly prevalent among pregnant women, lactating mothers, neonates, and/or exclusively breastfed infants. Increasing the dose of antenatal vitamin D supplementation may be considered, if similar findings are seen in larger community-based studies.

Previously, one-third of infants have been reported to have vitamin D levels <10 ng/mL[8] Fetal and newborn concentrations of 25 (OH) D depend on and correlate with maternal serum levels. Thus, newborns of vitamin D- insufficient mothers are at a greater risk of developing vitamin D deficiency.[10] Although there was no significant difference in vitamin D levels among the two groups in this study, it suggests that vitamin D levels are low among the normal neonate population in India and the mothers. In a similar study conducted by Singh, et al.[11] , it was found that 85.7% of the neonates were vitamin D- deficient. Other studies [9,12] also show that majority of the neonates have vitamin D deficiency even in tropical climates.
The study population was small and selective because we did not include extreme, early, and moderate preterm babies as seizures are less common in these babies and we would not get matched controls. This study needs to be done in a larger sample to find the status of vitamin D levels among mothers and babies in the Indian population.

Conclusion

The present study concluded that hypovitaminosis D in mothers is also associated with hypovitaminosis D in neonates. There is a need to assess the vitamin D status of pregnant and lactating women and to consider routine vitamin D supplementation or to increase the dose of vitamin D supplementation among pregnant and lactating women in this region. Routine vitamin D supplementation among healthy newborns also need to strengthened.

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