

## Study of incidence of hypocalcemia in infants admitted with seizures in a tertiary care hospital

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### ABSTRACT

**Background:** During growth, bone mass increases faster than the body weight, which results in increased demand of calcium. Hypocalcemia, seen in postneonatal infants, is related to poor oral intake, low level of Vitamin-D, familial causes, sepsis, and multiorgan failure. **Objective:** The objective of this study was to study the incidence of hypocalcemia in infants admitted with seizures. **Materials and Methods:** This prospective study was carried out in a tertiary care hospital, Indore, Madhya Pradesh, in infants of age 1 month–1 year, presenting with seizures. Details about age, sex, dietary history, exposure to sunlight, birth order, gestational age, type of seizures, its duration, and frequency were noted. All relevant clinical investigations were done. **Results:** A total of 54 infants were enrolled according to the study design among which, 19 patients (35.15%) had hypocalcemic seizures while 16 of them were below 6 months of age having increased alkaline phosphatase level and low serum phosphorus level which corresponds to Vitamin-D deficiency. The second common cause was febrile seizures 25.92% (n=14) and rest were of infective etiology. **Conclusion:** Hypocalcemia is a very common cause of seizures in infants and its association with Vitamin-D deficiency should be seen in every case.

**Key words:** Hypocalcemia, Seizures, Vitamin-D

Seizures are common in pediatric age group and approximately 4–10% of children experience at least one episode of seizure in the first 16 years of age [1]. Calcium plays an important role in intracellular signaling and proper functioning of intracellular and extracellular processes including muscle contraction, nerve conduction, and hormone release. During growth, bone mass increases faster than body weight, which results in increased demand of calcium. Along with calcium, phosphorus is also an essential component of bone and is necessary for skeletal mineralization.

When serum calcium is decreased, parathyroid hormone is secreted from parathyroid gland which leads to calcium absorption and release of calcium and phosphorus from bones and excretion of phosphorus and bicarbonate in urine to maintain serum calcium level. Hence, in Vitamin-D deficiency and/or decreased calcium intake, we find low serum calcium, increased alkaline phosphatase level, and decreased phosphorus level.

Hypocalcemia is seen in postneonatal infants, which is related to poor oral intake of calcium, low level of Vitamin-D, familial causes, sepsis, multiorgan failure, etc. In the 1930s, the role of Vitamin-D, regarding calcium regulation, was detected and its synthesis with exposure to sunlight was highlighted in relation to the epidemic of rickets in that era [2,3]. Since the 1970s, a lot of cases of hypocalcemic seizures in infants appeared in the

literature and were diagnosed due to hypovitaminosis-D [4]. Similar studies found low level of Vitamin D in hypocalcemic seizures in breastfed infants [5].

Due to increased incidence and burden of disease in community, some countries (US, Canada) implemented the policy of supplementation of Vitamin-D to all breastfed infants. It seems that we are entering in new epidemic. The objective was to find the incidence of hypocalcemia as a cause, in infants admitted with seizures and to study the level of phosphorus and alkaline phosphatase level in hypocalcemic seizures.

### MATERIALS AND METHODS

This prospective study was conducted in the Department of Pediatrics of a tertiary care hospital, Indore, over a period of 1 year. After taking informed consent from the parents and ethical committee approval, we have included infants from 1 month to 1 year of age having episodes of seizures. Those patients, who were presented with seizures and later on diagnosed as having brain tumor, cranial malformations, post-traumatic seizures (within 24 h of traumatic event), and neurometabolic and neurodegenerative disorders were excluded from this study.

According to standard references, total serum calcium level of 8.8–10.8 mg/dl (2.2–2.7 mmol/l) was considered as normal

and decrease in total plasma calcium concentration of <8.8 mg/dl was considered as hypocalcemia. Seizure manifestation was seen when serum calcium level decreases below 7 mg/dl. In general, total serum calcium level provides a satisfactory assessment of physiologic calcium. However, there are only few clinical situations in which total calcium measurement is not adequate, such as hypoalbuminemia, nephrotic syndrome, liver diseases, capillary leak, and protein-losing enteropathies. In infants, serum phosphorus level 3.8–6.5 mg/dl (1.25–2.10 mmol/L) was considered as normal. Any serum phosphorus level <3.8 mg/dl was considered below normal value. Normal serum alkaline phosphatase level in infants was 145–420 IU/L.

Blood samples were taken with full aseptic precautions and apart from routine investigations (complete blood count), sent for serum calcium, phosphorus, and alkaline phosphatase level estimation. Principle of the estimation of calcium was bichromatic end point technique, inorganic phosphorus by Gomorris method, and alkaline phosphatase level by P-nitrophenyl phosphate method. With above principles, tests were carried out by an autoanalyzer. Cerebrospinal fluid analysis was done in patients with suspicion of infective etiology. Whenever required, computed tomography and magnetic resonance imaging scan of infants were done to establish the diagnosis.

Along with birth order, mode of delivery, feeding history, dietary history of mother (vegetarian/non vegetarian) and exposure to sunlight during pregnancy and breastfeeding was recorded. History and observations were done according to the type of seizures, whether generalized/focal, number of seizure episodes, and approximate time duration of seizures were noted.

## RESULTS

According to the study design, 54 infants of seizures were admitted during the period of 1 year. From 54 cases of seizures, 19 infants (35.15%) were of hypocalcemic seizures (serum calcium <7 mg/dl) and 35 (64.85%) infants had seizures due to other causes. From 54 infants of seizures, 35 (64.85%) were male and 19 (35.15%) infants were female (Table 1). Of 54 infants, 23 (42.59%) were below 3 months of age, 13 (24.07%) were between 4 months and 6 months of age, and 18 (33.33%) infants were above 6 months of age. From 19 cases of hypocalcemic seizures, 16 cases were below 6 months of age, two cases between 6 and 9 months, and only one case was seen above 9 months of age (Table 2). The second most common cause of seizures was febrile seizures (n=14 infants, 25.92%). Other common causes were pyogenic meningitis (n=04, 7.40%), bronchiolitis (n=02, 3.70%), and bronchopneumonia (n=03, 5.55%). One case of perinatal hypoxic insult presented with seizures 1<sup>st</sup> time in 11 months of age. His milestones were slightly delayed.

In infants with seizures due to other causes, one infant was of 7 months of age, breastfed, serum calcium level 7.6 mg/dl, PO<sub>4</sub> level 4.0 mg/dl, and alkaline phosphatase level 895 IU/L had focal seizures, five episodes, lasting for <3 min. He was diagnosed as case of rickets and had radiological features of rickets. Another

**Table 1: Seizure distribution (age wise)**

Patients	Up to 3 months (%)	4–6 months (%)	More than 6 months (%)
Hypocalcemia	9 (16.66)	7 (12.96)	3 (5.55)
Others	14 (25.92)	6 (11.11)	15 (27.77)
Total	23 (42.59)	13 (24.07)	18 (33.33)

**Table 2: Seizure distribution (diagnosis)**

Diagnosis	n (%)
Hypocalcemic seizures	19 (35.15)
Febrile seizures	14 (25.92)
Pyogenic meningitis	4 (7.40)
Bronchopneumonia	3 (5.55)
Septicemia	2 (3.70)
Dyselectrolytemia	2 (3.70)
Bronchiolitis	2 (3.70)
Aseptic meningitis	1 (1.85)
Encephalitis	1 (1.85)
Intraventricular hemorrhage	1 (1.85)
Post-traumatic subacute subdural hemorrhage	1 (1.85)
Perinatal hypoxic insult	1 (1.85)
Non-communicating hydrocephalus with meningitis	1 (1.85)
Cerebral infarct	1 (1.85)
Rickets with hypocalcemia	1 (1.85)
Total	54 (100)

patient from other seizure group was of age 2.5 months, female, breastfed, serum calcium level 8.2 mg/dl, PO<sub>4</sub> level 2.7 mg/dl, and alkaline phosphatase level 578 IU/L. She had focal seizures seven episodes, lasting for 5 min. She was diagnosed as bronchiolitis. This indicates that these two patients, although having serum calcium level more than 7, might have had seizures due to hypocalcemia.

Majority of infants diagnosed as hypocalcemic seizures were breastfed (total 14, i.e., 73.68% of 19 patients); three infants were on top fed (15.78%) and two infants were both mixed top and breastfed (10.52%). Of 19 infants of hypocalcemic seizures, only five mothers were on occasional non-vegetarian diet. None of them gave a history of ingestion of fish in their diet which is a rich source of Vitamin D. Lack of exposure to sunlight was found in six mothers due to wearing burka. Other four mothers, although not wearing burka, had also given a history of no exposure to sunlight. In three infants of these mothers, alkaline phosphatase level was more than 1000 IU/L.

From 54 infants of seizures, serum calcium <7 mg/dl was found in 19 infants, between 7.0 and 8.8 mg/dl was found in 18 infants, and >8.8 mg/dl was found in 17 infants. A total of 26 infants had serum phosphorus <3.8 mg/dl, and 11 of 19 infants of hypocalcemic seizures had serum phosphorus <3.8 mg/dl. Of the remaining eight infants, five had serum phosphorus in the lower limit of normal range (3.9–5.1 mg/dl). Total 15 of 35 infants of other seizure groups (other than hypocalcemic seizures) had serum phosphorus level <3.8 mg/dl.

Serum alkaline phosphatase level was done in 42 infants and it

was more than 420 IU/L in 15 infants (78.94%) of hypocalcemic seizures. Serum alkaline phosphatase level >800 IU/L was found in five infants, and in other five infants, enzyme level was >1000 IU/L. Of 23 infants of other seizure groups, enzyme level was >420 IU/L in 10 infants. Of these 10 cases, two cases of bronchiolitis, one case of pneumonia, and one case of febrile seizure had calcium level less than normal (<8.8 mg/dl), and in all these four cases, serum phosphorus level was below normal. These findings suggest subclinical cases of Vitamin D deficiency.

Of 19 infants, 14 infants of hypocalcemic seizures had <5 episodes of seizures (73.68%), and of 6 infants of focal seizures, five had <5 episodes (Table 3). Only one case of focal seizures had 10 episodes and time duration of each seizure was <5 min. Seizures duration <5 min was seen in 14 (73.68%) infants of hypocalcemic seizures (n=19). Of 13 generalized hypocalcemic seizures, nine infants had <5 episodes and eight of nine generalized seizure episodes were of <5 min time duration (Table 3).

## DISCUSSION

Calcium requirement in the first 6 months is 210 mg/day and 7–12 months is 70 mg/day. Calcium deficiency is observed in infants and children receiving inadequate diet having <200 mg elementary calcium per day. Breast milk provides adequate calcium (28 mg/100 ml) while Vitamin-D plays crucial role in calcium absorption. Vitamin-D is synthesized in the skin by ultraviolet light from sun by its precursor 7-dehydrocholesterol. In the absence of Vitamin-D, only 10–15% of dietary calcium and 55–60% of phosphorus are absorbed. In our study, the incidence of hypocalcemic seizures was 35.5% (n=19 of total 54 cases) in children of 1 month–1 year of age admitted with seizures.

Of these 19 cases, total of 15 infants (78.95%) can be suspected due to Vitamin D deficiency. All these infants had serum calcium level <7.0 mg/dl, 15 infants had serum alkaline phosphatase level more than 420 IU/L and low S. phosphorus level (nine infants having <3.8 mg/dl and three infants in the lower side of normal). Of these, 12 infants were exclusively on breastfeeding. This correlates with the study of Agrawal *et al.* of the Vitamin D deficiency in breastfed infants [6]. 10 mothers had definite evidence of the lack of exposure to sunlight (six women wearing burka). This correlates with the study of Henderson *et al.* regarding Vitamin D deficiency due to limited exposure of sunlight, in etiology of Asian rickets [7,8]. Similar study by Hatun *et al.*, by evaluation of medical records of infants, found 79% of children of Vitamin D deficiency and rickets presented with hypocalcemic seizures [4].

Seizures in infants were brief in duration (mostly lasting <5 min), most seizures had <5 episodes similar to the finding of Agrawal *et al.* [9]. Balsubramanian *et al.*, in his study of 50 cases

of the hypocalcemic seizures in children aged 2–6 months (mean age 3.8 months), found 13 cases of Vitamin D deficiency in exclusively breastfed infants [10]. However, the study of the etiology of pediatric seizures by Taherian *et al.*, in 200 infants, found febrile seizures as most common cause (82%) and hypocalcemic seizures in only 2% children. This was due to children of higher age group in that study (3–102 months of age with the mean age of 23 months). This age group is the most common age of febrile seizures [11–13].

A total of 18 infants of seizures due to other causes also had S. calcium level <8.8 mg/dl (less than the normal limit for 1 year). Of these, 10 infants have S. alkaline phosphatase >420 IU/L and five patients had S. phosphorus <3.8 mg/dl. These cases indicate subclinical Vitamin D deficiency and correlate with the study by Holick *et al.* [14]. Three cases of bronchopneumonia and two cases of bronchiolitis had serum calcium level less than normal (8.8 mg/dl). This indicates extraskelatal manifestation of hypocalcemia (weakness of thoracic muscles with softening of rib cage results in defective ventilation with respiratory obstruction and infection). Vice versa, infections may lead to hypocalcemia.

In our study, in five cases above 4 months of age, we found radiological evidence of rickets in their wrist/knee X-rays (widening of growth plate, cupping, and frying) and one case of 1.5 months age had generalized rarefaction of bones in wrist X-ray. This correlates with the finding of Schneider *et al.* [15]. Due to increased metabolic demand of rapid growth, symptomatic hypocalcemia occurs even before the appearance of radiological changes. This probably explains why radiological changes were observed in only five cases in our study and only in two cases of Balsubramanian *et al.*

Mehrotra *et al.*, in the study of 60 infants of hypocalcemic seizures (15 days–6 months of age), found low level of Vitamin D (<10 ng/ml) in 54 infants, concluding Vitamin D deficiency as a major cause of hypocalcemic seizures in infancy [16]. Incidence of hypocalcemia as a cause of seizures in our study was 35.15% (n=19) and in 78.95% (n=15) of these infants, investigation findings suggest Vitamin D deficiency.

In view of the above similar observations, our study suggests hypocalcemia as a major cause of seizures in early infancy and Vitamin D deficiency should be the most important cause behind it. Limitations of this study was that we could not estimate the serum Vitamin-D level as cause behind hypocalcemic seizures due to its high cost and lack of availability of the laboratory facility.

## CONCLUSION

Hypocalcemia is a very common cause of seizures in infants having strong association with Vitamin D deficiency. As in other Western countries, where Vitamin D supplementation is recommended during infancy, further studies should be done with laboratory confirmation of Vitamin D level, to establish a policy regarding supplementation of calcium and Vitamin D in Indian infants.

**Table 3: Hypocalcemic seizures and its time of duration**

Seizure type	>5 episodes	<5 episodes	>5 min	<5 min
Generalized	9.0 (40.36)	4.0 (21.05)	8.0 (42.10)	5.0 (26.31)
Focal (%)	5.0 (26.31)	1.0 (5.26)	6.0 (31.57)	0.0
Total (%)	14.0 (73.68)	5.0 (26.31)	14.0 (73.68)	5.0 (26.31)

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