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Frequency of Hypocalcemic Fits in Children 2 Months to 2 Years of Age, Presenting with the First Episode of Afebrile Seizures at Hospital Settings in Urban Pakistan: A Cross-Sectional Study

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Abstract

Introduction: Seizures are common in the pediatric age group, occurring approximately 10% of children. Hypocalcemia is one of the most common metabolic causes of afebrile seizures. The objective of the study was to determine the frequency of hypocalcemic fits in children presenting with the first episode of afebrile seizures from 2 months to 2 years of age. **Methods:** The study was conducted at the Aga Khan hospital Karachi and its three secondary hospitals including the following sites of Kharadar, Hyderabad, and garden. It was a cross-sectional study. The duration of the study was of 6 months from 18th July 2017 to 18th Jan. 2018. All patients who fulfill the inclusion criteria and visited the Pediatric medicine Department of Aga Khan Hospital, Karachi, and its secondary hospitals were included in the study after ethical approval and informed and written consent. A brief history was taken, clinical examination was done and serum calcium level was sent to the institutional laboratory to reach the outcome *i.e.* hypocalcemic fits. **Result:** A total of 85 children presenting with the first episode of afebrile seizures were included. Total of 45 patients (52.98%) were males & 40 patients 2 (47.1%) were females with the mean age were 10.5824 ± 6.84907 months. The hypocalcemic fits were seen in 21 children (24.7%). **Discussion:** Hypocalcemia is a common cause of afebrile fits in children. Inadequate sun exposure, early age, male gender, low weight, and illiteracy are major risk factors for hypocalcemia.

1. Introduction

In children, hypocalcemia is defined as a total serum calcium concentration of less than 2.1 mmol/L (8.5 mg/dL) [1]. Seizures are common in the pediatric age group and occur in approximately 10% of children [2]. Amongst the various etiologies; hypocalcemia is a major biochemical cause of seizures in infancy in developing countries [3]. It constitutes 25.6% of afebrile seizures in children [4]. In a local study, hypocalcemia accounted for 68.3% of afebrile seizures [5].

The presence of seizure does not constitute a diagnosis but it is a symptom of an underlying central nervous system disorder due to systemic or biochemical disturbances [6]. Hypocalcemia in children may manifest as tetany, seizures, muscle cramps, and paresthesias [7]. The central nervous system irritability from hypocalcemia can cause anticonvulsant-resistant seizures. Such seizures often are brief, lasting a few seconds or minutes, but may recur frequently. Initially, there may be no postictal phase. Rarely, it may present with stridor or cyanosis from laryngospasm. Arrhythmias are even rarer. Electrocardiography may reveal a prolonged QTc interval. Most patients who have mild hypocalcemia are asymptomatic [8].

Hypocalcemia is associated with poor outcomes as measured by either survival or length of intensive care stay [9]. Infants fed with buffalo or cow's milk or formula containing a high amount of phosphate are also low in calcium because phosphate decreases the absorption of calcium. Balasubramanian *et al.* [10] in India identified indoor confinement during the day, living in urban areas with tall buildings, and the use of sunscreen as major risk factors for hypocalcemia. In another study, fresh unfortified milk, inadequate exposure to sunlight, lower maternal educational status, and large family size as risk factors for hypocalcemia.

Acute hypocalcemia is an emergency that requires prompt attention, and patients with symptomatic hypocalcemia should be treated immediately because of the highly associated morbidity and mortality. Treatment with intravenous calcium is the most appropriate therapy. Hypocalcemic seizures should be treated with calcium replacement, while AEDs are typically not needed. AEDs may abolish both overt and latent tetany, whereas hypocalcemic seizures may remain refractory [11]. There is a shortage of data in the pediatric population regarding the frequency of hypocalcemia in afebrile seizures. This study will help us to find out the frequency of hypocalcaemic fits to look into the consideration of empiric I/V calcium in afebrile fits patients that did not respond to anticonvulsant drug. Because in developing countries like Pakistan; it is worthwhile to give empiric I/V calcium in non-responsive afebrile fits. The benefit to the patient will be the

prevention of the harmful effects of hypocalcemic seizures. These results can be used in planning and priority setting.

1.1. Objectives

To determine the frequency of hypocalcaemic fits in children presenting with the first episode of afebrile seizures; from 2 months to 2 years of age.

1.2. Operational Definitions

1) Hypocalcemia: Serum calcium level <8.5 mg/dl in children.

2) Fever: temperature >100.4 F at the time of fits.

3) Afebrile seizures: Presence of fits in the absence of fever.

4) Fits (convulsions): abnormal involuntary jerky movements of any part of the body.

5) Hypocalcemic fits: fits which were due to low levels of calcium (<8.5 mg/dl) in blood.

6) Malnourishment (any child with weight for height/length above—2SD on WHO standardized growth chart was classified as malnourished).

7) Sun Exposure (sun exposure of less than 30 min/week was considered as inadequate).

2. Methods

2.1. Study Design

Cross-sectional study.

2.2. Setting

The Aga Khan Hospital Karachi and its secondary hospitals including the following sites:

1) Kharadar.

2) Hyderabad.

3) Garden.

2.3. Duration of Study

Was 6 months from 18th July 2017 to 18th Jan. 2018.

2.4. Sample Size

Sample size calculated using the WHO calculator taking the margin of error as 10%, confidence interval as 95%, and taking frequency of hypocalcemia (in afebrile fits) 68.3% (based on the previous study) [5], sample size came out to be 85.

2.5. Sampling Technique

Non-probability consecutive sampling.

Inclusion criteria:

Children from 2 months to 2 years of age having afebrile fits.

Exclusion criteria

Children having the previous history of fits/epilepsy.

Children with fever at the time of fits.

Ethical consideration

This study was post-graduation thesis project of Dr. Waseem and the thesis was approved by the College of Physicians and Surgeons, Pakistan. The study was also approved by Aga Khan University's Ethical review committee in 2017.

2.6. Data Collection Procedure

All children of the specified age group, who present with fits and no fever at the designated study sites, were enrolled in the study as per inclusion and exclusion criteria. All the data was recorded on a structured proforma; after reviewing the concerned medical records. Serum calcium levels were determined from the laboratory. Age, gender, and other relevant information were obtained from the caregiver. The patient was observed for fits and the duration of fits was documented. For confidentiality, all study participants were allotted a unique ID (other than hospital registration number) for study enrolment. Principle investigator himself was collecting the data. The study protocol was approved by the Ethical Review Board of Aga khan university hospital.

Informed consent was taken from the caregiver of the participant child. The caregiver was explained that participation in the study was voluntary, and no monetary compensation was given for the cost of an investigation.

2.7. Data Analysis Procedure

All the collected data were entered and analyzed in SPSS software version 19. Frequency and percentages were computed for categorical variables like gender, feeding pattern, sunlight exposure, nutritional status mother education, socioeconomic status, and hypocalcemic fits. Mean and the standard deviation was calculated for quantitative variables like age, weight, and height. Effect modifiers like age, gender, weight, feeding pattern, sunlight exposure, nutritional status, mother education, and socioeconomic status were controlled through stratification. Post-stratification chi-square test was applied by taking p-value < 0.05 as significant.

3. Result

A total of 85 children presenting with the first episode of afebrile seizures were selected to conduct this study. The mean age was 10.5824 ± 6.84907 months. The distribution of age is presented in Figure 1. Forty-five patients (52.98%) were males & forty patients (47.1%) were females. The mean weight was 6.67 ± 2.482 kg. The mean height was 69.74 ± 11.678 cms. The mean serum calcium level was 8.76 ± 1.7704 mg/dl. The distribution of serum calcium levels is presented in Figure 2. The descriptive statistics of weight, height, and serum calcium level are presented in Table 1.

Figure 1. Frequency distribution of age.
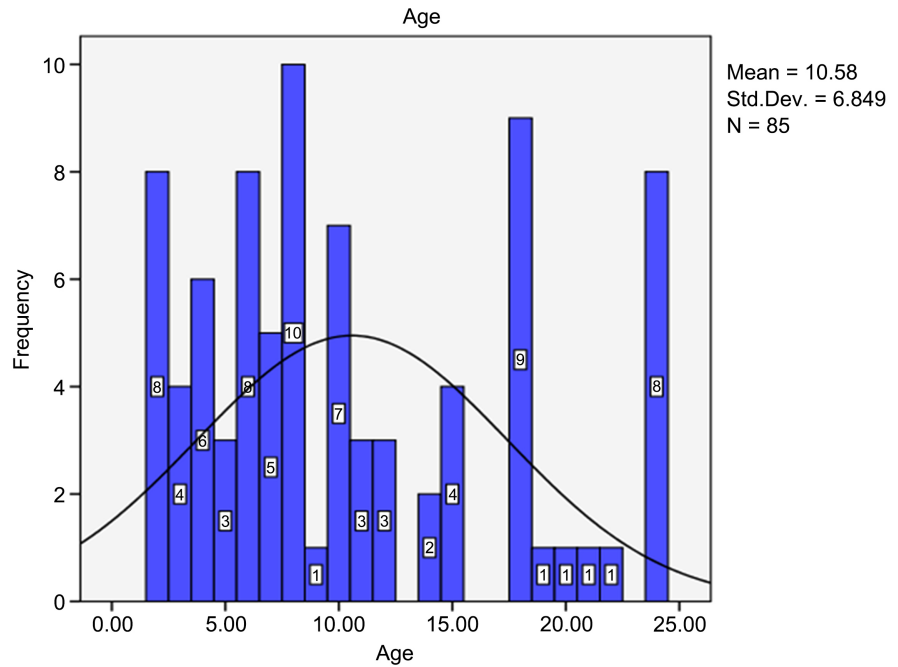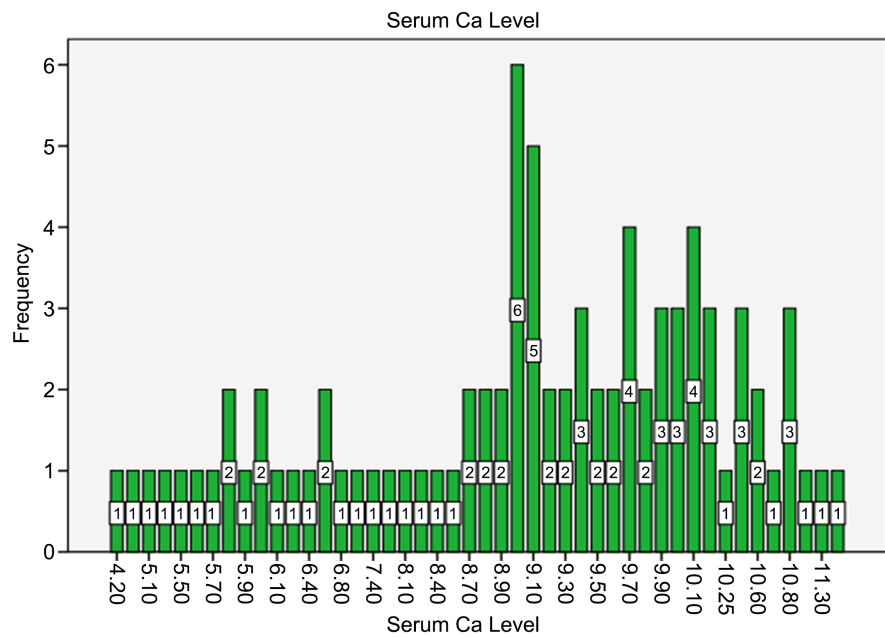

Figure 2. Frequency distribution of serum calcium level.

Table 1. Descriptive statistics of age, weight & serum calcium level.

Statistics	Weight (kg)	Height (cm)	Serum calcium level
Minimum	3	45	4.2
Maximum	16	96	12.5
Mean & Std. Deviation	6.67 ± 2.482	69.74 ± 11.678	8.76 ± 1.7704
Median	7.50	68.50	9.20

In our study, sun exposure was adequate in 57 patients (67.1%) and inadequate in 28 (32.9%). As shown in Table 2, 41 mothers (48.2%) were literate while 44 (51.8%) were illiterate. In socioeconomic status, 23 patients (27.1%) had income of <10,000 rupees/month, 52 (61.2%) had between 10,000 to 25,000 rupees/month and 10 (11.8%) had above 25,000 rupees/month (Table 2). 28 children (32.9%) were malnourished and 57 (67.1%) were well-nourished (Table 3). The feeding pattern was breast milk in 40 children (47.05%), formula milk in 39 (45.88%), and fresh milk in 6 (7.05%), as shown in Table 3. The outcome *i.e.* hypocalcemic fits were seen in 21 children (24.7%) presenting with the first episode of afebrile seizures, as shown in Table 4.

The frequencies of age groups, gender, weight, height, feeding pattern, sunlight exposure, nutritional status, mother education, socioeconomic status was calculated according to hypocalcemic fits and are presented in Table 4, Table 5, and Table 6 respectively.

The stratification according to age groups, gender, weight, height, feeding pattern, sunlight exposure, nutritional status, mother education, socioeconomic status was done to observe the effect of these modifiers on hypocalcemic fits.

Hypocalcemia fits were common in children of the age group of 2 - 12 months (68%), predominant in male gender (53%), and children with the low weight falling in 3 - 9 Kg (75%) and also more common in children with inadequate sunlight exposure and illiterate mothers.

Table 2. Frequency distribution of sun exposure, mother's education, socioeconomic status.

SUN exposure	Frequency N = (85)	Percentage (%)
Adequate	57	67.1%
Inadequate	28	32.9%
Total	85	100%
Mother's Education		
Literate	41	48.2%
Illitrate	44	51.8%
Total	85	100%
Socioeconomic Status		
<10,000 Rupees/Month	23	27.1%
Between 10,000 to 25,000 Rupees/Month	52	61.2%
Above 25,000 Rupees/Month	10	11.8%
Total	85	100%

Table 3. Frequency distribution of nutritional status, feeding pattern, hypocalcemic fits.

Nutritional Status	Frequency N = (85)	Percentage (%)
Malnourished	28	32.9%
Well Nourished	57	67.1%
Total	85	100%
Feeding Pattern		
Breast milk	40	47.05%
Formula milk	39	45.88%
Fresh milk	6	7.05%
Total	85	100%
Hypocalcemic Fits		
Yes	21	24.7%
No	64	75.3%
Total	85	100%

Table 4. Hypocalcemia fits according to age, gender, weight, height.

Age months	Hypocalcemia fits		Total	P-Value
	Yes	No		
2 - 12 months	19 (22.35%)	39 (45.88%)	58 (68.23%)	
13 - 24 months	2 (2.35%)	25 (29.41%)	27 (31.76%)	**0.084**
Total	21 (24.70%)	64 (75.29%)	**85 (100%)**	

Gender	Hypocalcemia fits		Total	P-Value
	Yes	No		
Male	14 (16.47%)	31 (36.47%)	45 (52.94%)	
Female	7 (8.23%)	33 (38.82%)	40 (47.05%)	**0.146**
Total	21 (24.70%)	64 (75.29%)	**85 (100%)**	

Weight	Hypocalcemia fits		Total	P-Value
	Yes	No		
3 - 9 kg	20 (23.52%)	44 (51.7%)	64 (75.29%)	
10 - 16 kg	1 (1.17%)	20 (23.52%)	21 (24.70%)	**0.511**
Total	21 (24.70%)	64 (75.29%)	**85 (100%)**	

Height	Hypocalcemia fits		Total	P-Value
	Yes	No		
45 - 70 cms	17 (20%)	30 (35.29%)	47 (55.29%)	
71 - 96 cms	4 (4.70%)	34 (40%)	34 (40%)	**0.522**
Total	21 (24.70%)	64 (75.29%)	**85 (100%)**	

Chi Square test was applied. P-value ≤ 0.05 considered as significant.

Table 5. Hypocalcemia fits according to sun exposure, mother's education, nutritional status & socioeconomic status (n = 85).

Sun exposure	Hypocalcemia fits		Total	P-Value
	Yes	No		
Adequate	9 (10.58%)	48 (56.47%)	57 (67.05%)	
Inadequate	12 (14.11%)	16 (18.82%)	28 (32.94%)	0.011
Total	21 (24.70%)	64 (75.29%)	85 (100%)	

Mother's Education	Hypocalcemia fits		Total	P-Value
	Yes	No		
Literate	7 (8.23%)	34 (40%)	41 (48.23%)	
Illitrate	14 (16.47%)	30 (35.29%)	44 (51.76%)	0.115
Total	21 (24.70%)	64 (75.29%)	85 (100%)	

Nutritional Status	Hypocalcemia fits		Total	P-Value
	Yes	No		
Malnourished	8 (9.41%)	20 (23.52%)	28 (32.94%)	
Well Nourished	13 (15.29%)	44 (51.76%)	57 (67.05%)	0.566
Total	21 (24.70%)	64 (75.29%)	85 (100%)	

Socioeconomic Status	Hypocalcemia fits		Total	P-Value
	Yes	No		
<10,000 Rupees/Month	9 (10.58%)	14 (16.47%)	23 (27.05%)	
Between 10,000 to 25,000 Rupees/Month	12 (14.11%)	40 (47.05%)	52 (61.17%)	
Above 25,000 Rupees/Month	0 (%)	10 (11.76%)	10 (11.76%)	0.052
Total	21 (24.70%)	64 (75.29%)	85 (100%)	

Chi Square test was applied. P-value ≤ 0.05 considered as significant.

Table 6. Hypocalcemia fits according to feeding pattern (n = 85).

Feeding Pattern	Hypocalcemia fits		Total	P-Value
	Yes	No		
Breast Milk	11 (12.94%)	29 (34.11%)	40 (47.05%)	
Formula Milk	2 (2.35%)	4 (4.70%)	6 (7.05%)	0.356
Fresh milk	8 (9.41%)	31 (36.47%)	39 (45.88%)	
Total	21 (24.70%)	64 (75.29%)	85 (100%)	

Chi Square test was applied. P-value ≤ 0.05 considered as significant.

4. Discussion

Seizures are one of the most common neurological disorders in children. The first episode of epileptic seizure is always an anxiety-causing event for parents and it is the health professional's duty to know the best approach and recommendations to use in each case. Seizures are common in the pediatric age group and one of the most common biochemical abnormalities causing seizures is hypocalcemia [12]. Hypocalcemia is emerging as a very common problem perhaps due to a lack of awareness of the morbid consequences [13].

In our study hypocalcemic fits were seen in 21 children (24.7%) presenting with the first episode of afebrile seizures, as compared to Khan *et al.* [5] study, 41 (68%) cases were hypocalcemic among the total study population of 60. In our study, the mean age was 10.5824 ± 6.84907 years as compare to Khan *et al.* [5] study the mean age at the time of admission was 7.5 ± 1.34 months. The majority of children (51.2%) were below 6 months. This is also consistent with results by Binmohana *et al.,* [12] and Humayun *et al.* [13] but is in contrast with Abanamy *et al.* [13] showing 39.2% patients less than 6 months of age. The present study noted slight male predominance 52.98% comparable with Khan *et al.* study showed (56%) and with Binmohana MA *et al.* [12] but Sharma *et al.* [14] found no gender difference. Inadequate exposure to sunlight is an important factor associated with the development of vitamin D-deficient rickets which in turn is a common cause in 73% of hypocalcemia in children [13] [15]. Our study highlighted this fact and the results showed (32.9%) children had inadequate sunlight exposure in contrast to Khan *et al.* [5] study showed the high number of children (68.3%) had poor exposure to sunlight. Balasubramanian *et al.* [10] in India identified indoor confinement during the day, living in urban areas with tall buildings, and the use of sunscreen as major risk factors for hypocalcemia. In another study, fresh unfortified milk, inadequate exposure to sunlight, lower maternal educational status, and large family size as risk factors for hypocalcemia, and these results are comparable with other studies [5] [14]. In the present study, the feeding pattern was breast milk in 40 children (47.05%), formula milk in 39 (45.88%) & fresh milk in 6 (7.05%), as compared to Khan *et al.* [5] study, 63.4% children received unfortified fresh milk, 34% breast milk and 2.4% formula milk. These results are also comparable with observations made by Temashek *et al.* [16]. Hypocalcemia is associated with poor outcomes as measured by either survival or length of intensive care stay [17]. Infants fed with buffalo or cow's milk or formula containing a high amount of phosphate are also low in calcium because phosphate decreases the absorption of calcium. In our study 28 children (32.9%) were malnourished and 57 (67.1%) were well nourished. However, Hatun *et al.* [18] observed that 83% infant who had vitamin D deficiency were exclusive breastfeed without supplemental vitamin D. Khan *et al.* [5] study showed 36.5% children with inadequate weaning and is comparable with results of Carvelt NF *et al.* [19] and Younas M *et al.* [20]. 32.9% of our study population was malnourished as compared to Khan *et al.* [9] study showed

seventy-two percent of the study population had malnutrition according to Gomez classification which is comparable to a study by Khattak *et al.* [21] The mean weight in the present study was 6.67 ± 2.482 kg and the mean height was 69.74 ± 11.678 cms. One previous study showed that 46% were low birth weight while 17% were preterm [10], the incidence of hypocalcemia is inversely proportional to gestational age and birth weight [21]. Recently, a study by Raazia Nawaz et al showed hypocalcemia prevalence of 51% in premature and low birth weight babies [22]. Hypocalcemia can be present with a wide variety of symptoms, the most important of which is seizures. In 90% of cases, seizure type was noted generalized tonic-clonic which was comparable with Sharma *et al.* [23]. Elevated alkaline phosphatase > 1000 1U/L was observed in 53.3% patient which is consistent with other studies [24]. This study showed that 76% of patients had radiological evidence of rickets in the form of cupping and fraying and is comparable with the results of New-ham *et al.* [25].

The limitation of this study was that we did not correlate hypocalcemia with magnesium levels.

5. Conclusion

Hypocalcemia is a common cause of afebrile fits in children. Inadequate sun exposure, early age, male gender, low weight, and illiteracy are major risk factors for hypocalcemia

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Ethics Approval and Consent to Participate

Aga Khan University Hospital ethical review committee approved the study in December 2017 with ERC number 5123-Ped-ERC-17.

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Authors' Contributions

WR, SA and HL contributed to drafting the article. WR conducted the research at hospitals. SU and AM conducted the research. WR and HL managed and analyzed data. KH designed and supervised the study. All authors approved the final version of the article for submission.

Competing Interests

The authors declare that they have no competing interests.

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