International Journal of Research in Medical Sciences
Ramdasi AV et al. Int J Res Med Sci. 2024 Jul;12(7):2398-2409
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20241889

Original Research Article

Clinical spectrum of hypocalcaemia in children

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Received: 26 April 2024
Revised: 03 June 2024
Accepted: 18 June 2024

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ABSTRACT

Background: Hypocalcaemia is a biochemical abnormality commonly seen in paediatric population with a multi-factorial etiology having varied presentation ranging from acute emergency to chronic diagnostic dilemma. We studied the clinical profile of infants and children presenting with hypocalcaemia from 0 to 12 years of age.
Methods: Clinical features, risk factors, precipitating factors, feeding/dietary practices of all children (0-12 years) visiting our tertiary care centre, from January 2019 to March 2020, diagnosed with hypocalcaemia were recorded and a correlation with serum calcium levels was studied.
Results: Out of 92 patients having hypocalcaemia majority 57 (62%) were males. Majority of participants belonged to age group of 6 months-2 years i.e. 40 (43.48%). The commonest presentation was convulsions present in 39 (42.39%) participants affecting more children less than 2 years of age; whereas majority of children above 2 years of age presented with growth impairment. Risk factors identified were perinatal risk factors, faulty feeding practices in infants, inadequate dietary calcium intake in children, inadequate sun exposure. Amongst the biochemical factors precipitating hypocalcaemia, alkalosis showed significant association (p value 0.016) with degree of hypocalcaemia; most common etiology was vitamin D deficiency and nutritional rickets.
Conclusions: Hypocalcemia plays vital role in infants and growing children because of its various implications on growth and development. Exposure to sunlight, vitamin D and calcium supplementation during pregnancy and lactation and infancy with good dietary calcium intake for children during their growth spurts can prevent complications. Health education and awareness of common risk factors for hypocalcaemia can prove helpful.

Keywords: Convulsion, Growth impairment, Hypocalcaemia, Nutritional rickets, Sun light exposure

INTRODUCTION

Hypocalcaemia is a common biochemical abnormality presenting as medical emergency as well as chronic diagnostic dilemma in infants and children.[1] Also hypocalcaemia is a common condition in our country because of low socioeconomic status, nutritional insufficiency, vitamin D deficiency, poor sunlight exposure and many other underlying factors. A study in India found the prevalence of hypocalcaemia in pregnant women was 66.4%, around 34% in infants and 58% in older children according to previous studies in Western Asia.[2,3]

Hypocalcaemia may be asymptomatic or can manifest with a variety of different symptoms varying with age of the child and developmental stage. Older children with hypocalcaemia present with tetany, paraesthesia, carpopedal spasm and laryngospasm, and seizures are less common.[1] Neonatal hypocalcaemia is often asymptomatic and when the clinical features are present, they tend to be nonspecific.[4] The signs and symptoms tend to mimic other neonatal disorders such as hypoglycemia, hypomagnesemia, sepsis and hypoxic ischemic encephalopathy etc. If untreated hypocalcaemia will lead to feeding intolerance, respiratory distress and intractable convulsions.[4]

Hypocalcemia is associated with various types of seizures including grand mal, petit mal and focal seizures. Previous studies have revealed that such patients show poor response to antiepileptic drugs if hypocalcemia is not treated before or simultaneously with antiepileptic drugs.[5] With proper approach unnecessary treatment with anti-epileptic drugs could be stopped. There are several effects of hypocalcaemia in the older children, including nutritional rickets.

The first step in maintaining a healthy calcium balance in body is adequate dietary intake of calcium. Indian diet is predominantly vegetarian, based on cereals and legumes, and is often deficient in milk and milk products which are a good source of calcium.[6] In India, ethnic difference of sunlight exposure is believed to be due to the decreased penetration of ultraviolet rays with increased skin pigmentation resulting in lower maternal vitamin D levels.

Though hypocalcaemia is a treatable condition but due to various socio demographic and nutritional factors, in developing countries like India it remains important etiological factor for pediatric patients presenting to outpatient department and also in indoor admissions. This has got an impact on the growth and development of the child, in addition to posing extra demand on health care facilities. Due to varied clinical presentation, the diagnosis can be missed or delayed leading to poor outcome. Studies regarding same are scarce in developing countries.

Hence this study is conducted with objective of studying such etiological factors and correlating the severity of Hypocalcemia with clinical presentation along with its impact on growth and development. This will be of help in better management of cases of hypocalcaemia and will lead to better outcome.

METHODS

The study assessed the clinical profile of hypocalcaemia in children birth to 12 years of age, along with association between serum calcium levels with the sociodemographic and other risk factors.

It was a prospective observational study, conducted over a duration of 15 months from January 2019 to March 2020. Institutional Ethics Committee (IEC) permission was taken prior to commencement of the study.

The study enrolled 92 participants including infants and children from birth up to 12 years of age who have been attending to pediatric outpatient department and admitted in Pediatric Ward or Intensive care unit during study period at Hindu Hriday Samrat Balasaheb Thackeray Medical College and Dr. R. N. Cooper Hospital, a Tertiary care medical institute, were included after parental consent. Universal sampling technique was used. Parents who did not consent to participate in the study were excluded.

Data was collected through face to face interview using the predesigned proforma. The detailed patient history including demographic data, presenting complaints, birth history, feeding practices and sunlight exposure in terms of minutes per week and findings of anthropometry, general physical and systemic examination were noted. Socioeconomic class was defined as per modified Kuppuswamy socioeconomic scale. The subjects with confirmed hypocalcaemia were investigated further for the first line investigations i.e. serum phosphate and alkaline phosphatase (ALP). Radiological investigations including skeletal x-rays and chest x-ray obtained wherever applicable. The additional investigations were done for etiological diagnosis according to indications.

Definitions[7,8,9,10]

Inadequate weaning: not on adequate diet or semisolid diet other than milk after age of 6 months.

Sun exposure: sun exposure in children was estimated approximately on average weekly exposure to face and head.

Inadequate sun exposure: weekly sun exposure to head and face for less than 30 min/week.

Anthropometry: nutritional status of each subject was assessed by measuring weight for age, height/length for age, weight for height/length and mid-upper arm circumference.

Severe acute malnutrition: cut off used as weight for height/length <-3 SD of the WHO standards or mid upper arm circumference (6 to 60 month old children) <11.5 cm.

Moderate acute malnutrition: weight for age between -3 and -2 Z scores below the median of the WHO child growth standards.

Short stature: height/length less than 2 SD of the mean for age

Low height for age (stunting) is a known indicator of chronic malnutrition.

Biochemical measurements

In all our study participants, serum calcium, phosphate, and alkaline phosphatase (ALP) were measured. Serum calcium was measured by calorimetric method. The normal values were defined as:

Serum calcium

In children, serum calcium >2.1 mmol/l (8.5 mg/dl).

In term infants, total serum calcium concentration >2 mmol/l (8 mg/dl) or ionized fraction of less than 1.1 mmol/l (4.4 mg/dl).

In preterm infants, total serum calcium concentration>1.75 mmol/l (7 mg/dl).

Serum phosphate and ALP were determined by photometric analysis. Normal range for serum phosphate was 4-7 mg/dl. The upper limit of normal serum ALP was 420 IU/l (infant-150-420 IU/l; 2 to 12 years-100-320 IU/l). The normal range for serum magnesium was 1.6-2.4 mg/dl and for serum albumin as 3 to 5.2 mg/dl.

Serum 25-hydroxyvitamin D (25OHD) and PTH levels were measured wherever applicable and parents were affordable. The normal range for serum PTH was 15-65 pg/ml. Based on widely accepted pediatric standards, a serum 25OHD levels were classified as: 1) Deficient – 25 OHD value of less than 10 ng/ml; 2) Insufficient- 25 OHD value between 10-20 ng/ml; 3) Sufficient- 25 OHD value more than 20 ng/ml.

Rickets

Rickets was diagnosed based on their clinical features and radiological features. Clinical features of rickets are:

General findings: Failure to thrive (malnutrition), listlessness, protruding abdomen, muscle weakness (especially proximal), hypocalcemic dilated cardiomyopathy, fractures (pathologic, minimal trauma).

Specific findings: Craniotabes, frontal bossing, delayed fontanelle closure, delayed dentition, no incisors by age 10 months, no molars by age 18, dental caries and chest findings like rachitic rosary, Harrison groove, respiratory infections and atelectasis. Skeletal deformities like scoliosis, kyphosis, lordosis, enlargement of wrists and ankles, valgus or varus deformities, anterior bowing of tibia and femur' coxa vara, windswept deformity and leg pain etc.

Hypocalcemic symptoms can manifest as tetany, seizures, stridor caused by laryngeal spasm. Radiological features of rickets include fraying of metaphysis, cupping of metaphysis, generalised reduction in bone density (osteopenia) and widening of growth plate etc.

Statistical analysis

The collected data was entered in Microsoft Excel. Data is represented in frequencies and percentages. Mean and standard deviation of quantitative variables is shown. Appropriate statistical tests are applied using SPSS software version 21 for analysis. The Chi square test is used for association and the student's t-test is used for comparison between the study variables. Significance is considered at $p<0.05$.

RESULTS

Our study included 92 confirmed cases of hypocalcaemia from 0 to 12 years of age and data is mentioned in tables in the form of frequency and percentage.

Table 1: Socio-demographic features of study population.

Socio-demographic factor	Frequency	Percentage
Gender		
Female	35	38.0
Male	57	62.0
Age groups		
<1 month	10	10.87
1 to 6 months	20	21.74
6 months to 2 years	40	43.48
2 years to 12 years	22	23.91
Religion		
Buddhist	1	1.1
Hindu	36	39.1
Muslim	55	59.8
Socioeconomic status		
Lower class	63	68.5
Lower middle class	23	25.0
Upper middle class	6	6.5
Total	92	100.0
Total	92	100.0

Male predominance was observed with 57 (62%) males. The majority of the participants i.e. 40 (43.48%) were in the age group of 6 months-2 years. The majority of study participants i.e. 55 (59.8%) belonged to Muslim religion and 63 (68.5%) patients belonged to lower socioeconomic class as per the Kuppuswamy classification (Table 1).

The most common presenting complaint was convulsions, seen in 39 cases (42.39%). Majority of patients were under 2 years of age and most common complaint was convulsions, seen in 35 out of total 70 cases (50%). 22 children were more than 2 years of age and most common complaint was impaired growth seen in 9 cases (40.91%), followed by skeletal deformities in 6 cases (27.27%). In children less than 2 years of age, most common acute clinical presentation was seizures in 35 (50%) cases. In children more than 2 years, most common finding was skeletal features of rickets in 8 (36.36%) cases, followed by short stature in 5 (22.73%) (Table 2). Majority of our study participants 44 (47.8%) had sun exposure less than 30 minutes/week, and only 21.7% had sun exposure more than 120 minutes/week. In children above 2 years of age, only 5 out of 70 i.e. 22.7% had history of taking adequate calcium in their diet. Only 12 (13%) out of 92 patients and 2 (2.1%) mothers of babies below 6 months of age had history of taking calcium or vitamin D supplements (Table 3).

Table 2: Presenting complaints and acute clinical findings amongst the study population.

Presenting complaints	Frequency (%)	In children <2 years (n=70) (%)	In children >2 years (n=22) (%)
Convulsions	39 (42.39)	35 (50)	4 (18.18)
Febrile illness	29 (31.52)	25(35.71)	4 (18.18)
Impaired growth	20 (21.73)	11 (15.71)	9 (40.91)
Skeletal deformities	13 (14.13)	7 (10.0)	6 (27.27)
Delayed milestones	13 (14.13)	10 (14.29)	3 (13.63)
Tetany	5 (5.43)	1 (1.42)	4 (18.18)
Jitteriness	3 (3.26)	3 (4.28)	0 (0)
Noisy breathing	2 (2.17)	2(2.85)	0 (0)
Weakness of both lower limbs	1 (1.08)	0 (0)	1 (4.54)
Acute clinical findings	**Frequency (%)**	**In children <2 years N (%)**	**In children 2-12 years N (%)**
Seizures	39 (42.39)	35 (50.00)	4 (18.18)
Skeletal features seen clinically	25 (27.17)	17 (24.28)	8 (36.36)
Short stature	11 (11.96)	6 (8.57)	5 (22.73)
Jitteriness	7 (7.61)	6 (8.57)	1 (4.55)
Tetany	5 (5.43)	1 (1.43)	4 (13.64)
Stridor	3 (3.26)	3 (4.28)	0(0)
Transient tachypnea of newborn	1 (1.09)	1 (1.43)	0 (0)
Arrhythmia	1 (1.09)	1 (1.43)	0 (0)
Total	92 (100)	70 (100)	22 (100)

Table 3: Dietary history, sun exposure, calcium and vitamin D supplementation and significant past history amongst the study population.

	Frequency (n=92)	Percentage
Sun exposure (minutes/week)		
<30 minutes	44	47.8
30 to 120	28	30.4
>120	20	21.7
Feeding history in less than 2yrs of age		
Exclusive breastfeeding till 6months of age	29	37.66
Formula feeding	17	22.07
Fresh diluted milk	28	36.36
Prolonged parenteral nutrition	3	3.89
Faulty feeding practices in neonates and children less than 2 years		
Delayed weaning	10	14.2
Improper dilution of top milk	34	48.57
History of taking adequate calcium in diet in children more than 2 years of age	**Frequency (n=22)**	**Percentage**
Yes	5	22.7
No	17	77.2
Total	22	100
Calcium/vitamin D supplements	**Frequency (out of)**	**Percentage**
Study population - children	12 (out of 92)	13.0
Mothers of study population (babies <6 months of age)	2 (out of 30)	2.1
Past history		
Convulsions	13	14.1
NICU admission	10	10.9
Febrile Seizures	8	8.8
Taking antiepileptic medications	4	4.4
Regression of milestones	2	2.2
Vitamin D deficiency rickets	1	1.1

Table 4: Anthropometric status and head to toe examination findings of the study population.

	Frequency	Percentage
Anthropometry		
SAM	5	5.4
MAM	22	23.9
Short stature	11	12.0
Normal	51	55.4
Head to toe examination		
Frontal bossing	42	45.7
Delayed dentition	14	15.2
Rachitic rosary, Harrison sulcus	27	29.3
Pigeon shaped chest	3	3.26
Wrist widening	40	43.5
Pot belly	15	16.3
Bow legs	23	25.0
Double malleoli	17	18.5

Table 5: Perinatal, clinical and biochemical risk factors precipitating the clinical presentation of hypocalcaemia amongst study population.

Variables	Neonates (n=10)	Percentage
Perinatal factors		
Prematurity	4	40
Birth asphyxia	2	20
Maternal diabetes	2	20
IUGR	0	0
No any perinatal risk factor	2	20
Clinical precipitating factors		
Fever	17	65.38
Tachypnea	8	30.76
Intense physical exercise	1	3.84
Biochemical precipitating factors		
Hypoalbuminemia	37/92	40.2
Alkalosis	5/19	5.4

About 22 patients (23.9%) had MAM, 5 (5.4%) had SAM 11 (12%) patients had short stature.

Most of the study participants had more than one finding, maximum patients had frontal bossing i.e. 42 (45.7%) (Table 4). Amongst 10 neonates included, significant perinatal risk factors were present in 8 neonates. Fever was most common precipitating factor in 17 (65.38) patients (Table 5).

Maximum patients i.e. 63 (68.5%) had serum calcium levels between 7-8.5mg %. In one participant, urinary phosphate excretion was increased, with fractional excretion being 26.89% (normal <20%), confirming hypophosphatemic rickets. Ionic calcium levels were measured were low in 30 out of 30 participants and serum magnesium levels were low in 3 (42.8%) out of 7 participants.

Vitamin D levels were normal in only 4 (10.8) patients, who were already on vitamin D supplementation. The most common radiological finding was rib beading in 19 (20.7%) cases. One patient with osteogenesis imperfecta had multiple fractures in all 4 limbs. In 55 (61.1%) participants, other nutritional deficiencies were also observed along with calcium deficiency (Table 6).

Table 6: Laboratory parameters, radiological findings and other nutritional deficiencies amongst the study population.

	Frequency (n=92)	Percentage
Serum calcium		
Less than 6 mg%	2	2.2
6 to 7 mg%	27	29.3
7 to 8.5 mg%	63	68.5
Serum phosphorus		
Less than 4 mg/dl	36	39.1
4.1-7 mg/dl	54	56.6
More than 7 mg/dl	2	2.1
Fractional excretion of urinary phosphate	1	26.89
Alkaline phosphatase		
100-420 IU/l	29	31.5

Continued.

	Frequency (n=92)	Percentage
421-1000 IU/l	40	43.3
More than 1000 IU/l	23	25
Serum albumin		
Less than 3 g/dl	37	40.21
More than 3.1 g/dl	55	59.78
Total	92	100
Ionic calcium		
Less than 1.1 mmol/l	30	100.0
More than 1.2 mmol/l	0	0
Total	30	100
Serum magnesium		
Less than 1.7 mg/dl	3	42.8
More than 1.7 mg/dl	4	57.1
Total	7	100
Vitamin D		
Less than 10 ng/dl (deficiency)	14	37.8
10 to 20 ng/dl (insufficiency)	19	51.3
More than 20 ng/dl (sufficiency)	4	10.8
Total	37	100
Serum PTH		
10-65 ng/dl	5	14.7
More than 65 ng/dl	29	85.3
Total	34	100
Radiological findings		
Rib beading	19	20.7
Bowing of legs	15	16.3
Cupping of metaphysis	16	17.4
Fraying of metaphysis	6	6.5
Thinning of cortex of long bones	16	17.4
Others	5	5.4
Other nutritional deficiency		
Vitamin D insufficiency	19	34.5
Vitamin D deficiency	14	25.4
Dimorphic anemia	12	21.8
Iron deficiency anemia	6	10.9
Magnesium deficiency	3	5.4
Megaloblastic anemia	1	1.8

Table 7: Etiological diagnosis of hypocalcaemia in all the study participants.

Etiological diagnosis	Frequency	Percentage
Vitamin D deficient rickets (secondary to vitamin D underproduction)	34	36.90
Nutritional rickets (secondary to inadequate dietary calcium)	37	40.21
Vitamin D resistant rickets (secondary to defective vitamin D metabolism)	1	1.08
Hypophophatemic rickets (renal phosphate wasting)	1	1.08
Hypocalcaemia secondary to renal failure	2	2.17
Early onset neonatal hypocalcaemia	6	6.52
Late onset neonatal hypocalcaemia	4	4.34
Hypocalcaemia secondary to acid base disorders	5	5.43
Drug induced hypocalcaemia	4	4.34

Most common diagnosis was nutritional rickets in 37 (40.21%). Amongst those 5 who had hypocalcemia secondary to acid base disorders, 3 participants presented with acute respiratory illness and 2 had acute gastroenteritis (Table 7). Study participants were treated according to standard treatment protocols, and followed up after 1 month, 50 (54.3%) showed improvement in form of raised serum calcium levels and decreased

alkaline phosphatase levels, 15 participants (16.30%) had poor compliance with advised treatment, 25 participants (27.17%) did not follow up with us and 2 (2.2%) had mortality during their PICU stay owing to their underlying conditions (Table 8).

The mean serum calcium in study participants was 7.390±0.726 mg/dL, mean value of other parameters is as mentioned in Table 9.

No any significant association was seen between the presenting complaints and serum calcium levels of the patients. There was significant association between the exclusive breast feeding and severity of hypocalcaemia in less than 2 years, these were the cases whose mothers were not on any calcium vitamin D supplements. Significant association was seen between the delayed weaning, mean sun exposure per week, the presence of perinatal risk factors in neonates as compared infants in their post-neonatal period and alkalosis with degree of hypocalcaemia (Table 10).

Table 8: Final outcome of study participants after initial treatment.

Outcome	Frequency	Percentage
Improved	50	54.3
Poor compliance with treatment	15	16.30
Lost to follow up	25	27.17
Died	2	2.2
Total	92	100

Table 9: Laboratory parameters-descriptive statistics.

Laboratory parameter	frequency	Minimum	Maximum	Mean	Std. Deviation
Serum calcium	92	5.2	9.4	7.39	0.726
Serum phosphorus	92	2.3	9.6	4.74	1.40
Alkaline phosphatase	92	119	3155	826.02	663.300
Serum albumin	92	2.2	3.5	2.95	1.930
Ionic calcium	30	0.6	1.1	0.97	0.183
Vitamin D	37	3.2	38.9	13.93	8.79
Serum PTH	34	23.3	644.5	173.88	151.417
Serum magnesium	7	1.5	2.1	2.00	0.42

Table 10: Association between different study parameters and degree of hypocalcaemia.

Presenting complaints		**Serum calcium levels**		
	Frequency	**6-7 mg% (29)**	**7-8.5 mg% (63)**	**P value**
Convulsions	39	14	25	0.22
Febrile Illness	29	7	22	0.44
Impaired growth	20	5	15	0.51
Limb deformities	13	3	10	0.62
Tetany	5	1	4	0.71
Delayed milestones	13	5	8	0.56
Noisy breathing	2	1	1	0.86
Jitteriness	3	1	2	0.65
Feeding history	**Total**	**<7 mg% (25)**	**7-8.5 mg% (45)**	**P value**
Exclusive breastfeeding till 6m	29	17	12	0.021*
Formula feeds	18	4	14	0.16
Fresh milk	28	9	19	0.21
Prolonged parenteral nutrition	3	2	1	0.18
Faulty feeding practices	**Frequency**	**Less than 7 mg% (29)**	**7-8.5 mg% (63)**	**P value**
Delayed weaning	21	11	10	0.019*
Improper dilution	42	14	28	0.732
Mean sun exposure	**Less than 7 mg% (29)**	**7-8.5 mg% (63)**	**P value**	
Hrs/ week	0.37±0.258	2.11±1.26	<0.0001	
Clinical findings	**Less than 7mg%**	**7-8.5 mg%**	**Total**	
Seizures (GTCS)	12	27	39	
Features of rickets	6	19	25	
Short stature	4	7	11	
Arrhythmia	1	0	1	

Continued.

Presenting complaints		Serum calcium levels		
Transient tachypnea of newborn	0	1	1	
Carpopedal spasm	2	3	5	
Stridor	1	2	3	
Jitteriness	2	5	7	
Total	29	63	92	
P = 0.857, not significant				
Perinatal factors	**Frequency**	**S. calcium less than 7 mg%**	**S. calcium (7-8.5 mg %)**	**P value**
Prematurity	14	9	5	0.004*
Birth asphyxia	8	2	5	0.678
Maternal diabetes	3	2	1	0.183
Clinical precipitating factors	**Frequency**	**S. calcium less than 7 mg%**	**S. calcium (7-8.5 mg %)**	**P value**
Fever	17	4	13	0.714
Tachypnea	8	2	6	0.478
Exertion	1	0	1	-
Precipitating factors-biochemical	**Frequency**	**Less than 7 mg% (29)**	**7-8.5 mg% (63)**	**P value**
Hypoalbuminemia	37	18	19	0.988
Alkalosis	5	4	1	0.016*
Perinatal factors	**Neonates (n=10)**	**Other children (n=82)**	**Total**	
	Sr. Ca <7 mg% / Sr. Ca 7-8.5 mg%	Sr. Ca <7 mg% / Sr. Ca 7-8.5 mg%		
Yes	6 / 2	4 / 12	24	
No any perinatal risk factor	1 / 1	18 / 48	66	
Total	7 / 3	22 / 60	92	
P=0.0006, Significant				

DISCUSSION

Our study highlights the important clinical features and varied presentations of hypocalcaemia, which is an evolving and multi-factorial problem worldwide in children, owing to increased requirement of calcium in their growing periods.

Socio demographic risk factors

Male predominance (62%) seen in study participants, which is consistent with findings of other studies by Mohanna et al and Sharma et al.[3,1] Majority of the study participants i.e.40 (43.48%) participants were in the age group of 6 months-2 years. Our findings are consistent with other studies by Khan et al and Basatemur et al.[11,12] Majority of our study participants i.e. 63 (68.5%) belonged to lower socioeconomic class as per Kuppuswamy classification. Similar findings were reported by Agarwal et al in their study conducted in New Delhi and in a study by Mansoor et al, in which 72% participants belonged to lower socio-economic strata.[13,14] This can be attributed to that more educated parents can render their children better. Also, because these families live in overcrowded areas, exposure to sunlight is also affected. Lower per capita income further contributes to their malnutrition. Majority of study participants belonged to Muslim religion (59.8%), increased frequency of hypocalcaemia in Muslim community can be related to their concealing clothing and cultural practices.

Clinical presentation

The most common presenting complaint was convulsions in 42.39% of participants, Khan et al also reported most common presentation to be seizures in 85% of study population.[11] In 35 (50%) out of the 70 children aged less than 2 years, most common complaint was convulsions. In a study conducted by Bande et al, 35.15% patients presented with hypocalcaemic seizures and was commonest cause of infantile seizures. Mehrotra et al also reported that in infants, convulsion (60%) was most common presenting complaint, similar findings were reported in a study by Bitaraf et al.[15-17] Above 2 years of age, most common complaint was impaired growth seen in 40.91% cases, followed by limb deformities in 27.27% of cases. Mansoor et al also reported that above 2 years, most common complaint was growth retardation (45%).[14] These findings were similar to studies done by Agarwal et al and Khan et al.[13,11]

Hypocalcaemic symptoms present in two distinct periods, early childhood (most cases) and adolescence possibly because of higher metabolic demand for calcium during these periods of rapid bone growth.[18-20]

Past history

Our study highlighted about the importance of sunlight exposure in vitamin D synthesis and rickets prevention. The results showed that the majority of our study participants i.e. 47.8%, had sun exposure for less than 30 minutes per week. The findings were consistent with a study conducted by Ekbote et al where 42.9% children had sunlight exposure for less than 30 min per week.[21] These findings are also consistent with other studies by Miyako et al and Liaqat et al.[23,10] Aggarwal et al in a case control study found no any significant difference in the serum 25OHD level or sun exposure as measured by UV score among the cases and controls.[13]

Exclusive breastfeeding without vitamin D supplementation, inadequate weaning, use of formula milk/fresh milk with improper dilution were found to be the contributing factors for hypocalcaemia below 2 years of age. Though exclusive breastfeeding is recommended up to 6 months with all its beneficial effects on child survival, breast milk is not an adequate source of vitamin D, as it contains only about 20-60 IU/l of vitamin D while the RDA of vitamin D for infants is 200-400 IU/day.[23,24] Also lowered maternal levels may result in impaired acquisition of calcium by the neonate and thus infants can present with symptomatic hypocalcaemia after 2-3 month of age. Fresh milk (cow's milk) because of its high phosphorus content also leads to hypocalcaemia. Formula milk has higher calcium content, however, fractional calcium absorption is lower in formula fed infants and further improper dilution leads to decreased calcium bioavailability.[25] Our findings were similar to studies conducted by Khan et al, Hatun et al in Turkey and Balasubramanian et al, Mauskar et al and Marshal et al which concluded that adequate vitamin D supplementation to pregnant and lactating mothers and to exclusively breastfed infants is also helpful.[11,26-29] Study by Liaqat et al has shown improper and delayed complementary feeds are associated with hypocalcaemia.[10]

Above 2 years of age, 77.2% participants lacked calcium rich food items in their diet. Our findings were consistent with a study by Agarwal et al, Balasubramanian et al from Lucknow, India, and Pettifor et al from South Africa.[13,27,30] However, Thacher et al from Nigeria did not find any difference in calcium intake between cases and controls.[31]

History of taking anticonvulsant medications was seen in 4 (4.4%) study participants out of which 3 were on phenobarbital,1 on phenytoin. A study by Ali et al in Kuwait, reported that the anticonvulsant phenytoin and phenobarbitone may paradoxically exacerbate seizures when blood calcium is low either by affecting bone mineral density or by conversion of 25(OH) D3 into its inactive metabolites.[32] Similarly, Bitaraf et al reported positive drug history for hypocalcaemia with commonly implicated drugs being AEDs (e.g. phenytoin and phenobarbitone).[33]

Examination findings

In our study, 42.4% participants had malnutrition which is comparable to results of study conducted by Liaqat et al where 54% of their study participants had malnutrition.[10]

On general examination maximum patients had features of rickets, i.e. frontal bossing in 42 (45.7%) followed by wrist widening in 40 participants (43.5%), 23 (25.0%) had bowing of legs, 18.5% had double malleoli, with others having pot belly, delayed dentition. Pettifor et al in their study reported most common feature of rickets was frontal bossing (51%) followed by wrist widening (32%) and bow legs (12%) similar to our study. Findings were also consistent with study by Reddy et al.[30,34]

Most common perinatal risk factor for symptomatic hypocalcaemia was prematurity followed by birth asphyxia and maternal diabetes in similar proportion. Jeong et al in their retrospective study reported that early onset hypocalcemia is affected by many perinatal risk factors, including moderate to late preterm births, maternal diabetes.[35]

Risk factors precipitating the clinical presentation

Fever was found to be the most common precipitating factor for acute presentation of hypocalcaemia followed by tachypnea in study participants. It could be due to their physiological mechanisms. Similar observations were made in studies done by Kiran et al.[36] About 5 (5.4%) out of 19 participants showed alkalosis and hypoalbuminemia was seen in 37 cases (40.2%). Acid base disorders were found in 3% of the cases in a study conducted by Mnasoor et al. The blood pH, protein and anion level affect the total calcium leading to hypocalcaemia.[14]

Seizures were seen more commonly in children less than 2 years age; in 50% of cases as compared to 18.18% cases amongst 2 to 12 years age group. Kamate et al showed significant association between the seizures and young children below 2 years of age with hypocalcaemia.[37] Pettifor et al reported the presence of features of rickets in older children as compared to infants; this can be due to the more requirement of calcium for the growth and development of bones after 2 years of age.[30]

One infant in our study presented with febrile illness and cardiogenic shock, and also had severe hypocalcaemia. Hypocalcaemia predisposes to arrhythmias by affecting both depolarisation and repolarisation of cardiac myocytes. Similar to our study, in a study conducted by Gupta et al found severe hypocalcemia to be a sole cause of pulseless ventricular tachycardia who responded

dramatically to therapeutic doses of calcium and vitamin D.[38] Similar finding was reported by Maiya et al.[39]

About 37 (40.21%) study participants had hypoalbuminemia suggesting that it is associated with hypocalcemia. Hypomagnesemia was present in 3 out of 7 i.e. (42.8%) cases. Magnesium is required for the production and release of PTH, so hypomagnesemia, results in insufficient PTH production and secondary hypocalcaemia.[40]

Vitamin D levels were deficient in 14(37.8%) out of 37 study participants. A study conducted by Bosworth et al reported that hypocalcaemia was, present in 24% cases with vitamin D deficiency.[41]

Radiological finding

In our study, most common radiological findings were of rickets i.e. rib beading followed by cupping of metaphysis and thinning of cortex and bowing of legs. This is in consistent to a study by Erfan et al in North Yemen where 27% of children under five years had rickets.[42]

Etiological diagnosis

Most common etiological diagnosis was rickets in total 73 (79.34%) study participants, Bitaraf et al reported that the rickets was the commonest cause of hypocalcaemia in 72.4% children from one month to 14 years.[33]

In a study conducted by Mansoor et al chronic renal failure and rickets were most frequently associated with hypocalcaemia in their clinical setup.[14] Pure calcium deficiency has been reported to cause rickets, and studies including clinical trials have demonstrated healing with only calcium supplementation.[43]

Outcome

In our study, outcome after initial treatment was studied at 1 month follow up. Out of 92, 50 (54.3%) cases improved showed improvement in form of either normalization of biochemical or radio logical findings. 2 (2.2%) patients who had mortality, were cases of congenital heart disease with failure to thrive with sever hypocalcaemia. HI Khan et al also reported a mortality of 3% amongst children with hypocalcaemia, similar to our study.[11]

Association between different study parameters and degree of hypocalcaemia

A significant association was seen between the exclusive breast feeding and delayed weaning with degree of hypocalcaemia in less than 2 years of age. Khan et al reported that there was significant association between the faulty feeding practices and hypocalcaemia, similar to our study but it was statistically not significant.[11] A significant association was seen between the prematurity and level of hypocalcaemia.

As there is no significant association seen between the clinical presentation and severity of hypocalcemia, prompt workup of hypocalcaemia is mandated without waiting for severe symptoms such as seizures, tetany, stridor or cardiac arrhythmias which can be life threatening. India has burden of ‘twin nutrient deficiency’ i.e. both calcium and vitamin D deficiency, our study highlights importance of supplementation of both calcium and vitamin D to prevent hypocalcaemia. Early identification and treatment of precipitating factors can prevent life threatening complications of hypocalcaemia.

This study has few limitations. Sample size is small. Etiological diagnosis couldn’t be established in all cases due to unavailability of in house laboratory testing for special tests like serum vitamin-D level, serum PTH, ionic calcium and serum magnesium and unaffordability.

CONCLUSION

Children under 2 years of age are more prone for symptomatic hypocalcaemia. Nutritional insufficiency, inadequate sun exposure, exclusive breastfeeding without vitamin D and calcium supplementation, improper feeding techniques, rickets, lower socioeconomic status, malnutrition and perinatal risk factors are important causes for hypocalcaemia. While treating nutritional rickets either due to calcium or vitamin D deficiency, supplementation with both is necessary to get the adequate response. Thus, thorough knowledge regarding the modifiable risk factors and clinical implications of hypocalcaemia in children will help planning preventive and treatment strategies to improve immediate and long term outcome.

Recommendations

The study recommendations are as follows- 1) ensuring supplementation with vitamin D and calcium to pregnant and lactating mothers, and infants can prevent hypocalcaemia and its consequences. If on supplementation, optimal dosage and compliance for its adequate therapeutic effects should be checked; 2) good dietary calcium intake during child's growth spurts should be ensured; 3) direct exposure to sunlight, to ensure adequate production of vitamin D and it’s importance should be explained to all parents; 4) first contact pediatrician should be sensitized to identify varied presentations of hypocalcaemia, and manage timely with regular follow up; and 5) population should be made aware of common risk factors for hypocalcaemia through public health education measures.

ACKNOWLEDGEMENTS

Authors would like to thank Dean, for permitting to publish the study. Authors would like to thank Pediatric

faculties, Resident doctors and Nursing staff at H.B.T.M.C and Dr. R.N. Cooper Hospital, in helping and coordinating for the patient management. Authors would also like to thank the caregivers and children who took part in the study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ramdasi AV, Wade M, Inamdar NR. Clinical spectrum of hypocalcaemia in children. Int J Res Med Sci 2024;12:2398-409.