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Pediatric Hypocalcemia Clinical Presentations and Etiology: A Hospital-Based Study

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Abstract: Hypocalcemia is a common condition that is frequently encountered in laboratory and clinical settings, particularly in neonatal pediatric patients. Hypocalcemia in children is characterized by a blood calcium concentration below 2.1 mmol/L (8mg/dl) or an ionized fraction below 1.1 mmol/L (4.4mg/dl). What is the location? To determine the primary causes of hypocalcemia based on age group and to ascertain the predominant signs and symptoms associated with each cause of hypocalcemia. We conducted a cross-sectional study in Baghdad, Iraq, from April 1, 2017, to April 30, 2018. During this period, a total of 68 children with symptomatic hypocalcemia were admitted to the medical wards of the Children Welfare Teaching Hospital. The age of the patients varied between birth and 15 years. The collected data included the following variables: name, age, sex, gestational age, birth weight, consanguinity, feeding method, family history of the same disease, signs and symptoms, and any associated illnesses and anomalies. Comprehensive examinations were conducted on all patients, which involved analyzing serum levels of calcium, phosphorus, alkaline phosphatase, blood urea, creatinine, parathyroid hormone, vitamin D, magnesium, and albumin. Additionally, ultrasound scans of the abdomen were performed. However, specific cases underwent further tests, including a 24-hour collection of calcium and phosphorus, as well as X-rays of the wrist, skull, and chest. Selected cases also underwent MRI and CT scans. The majority of patients in this study had hypocalcemia at ages ranging from 1 to 5 years (28 out of 68, or 41.2%). Additionally, most of these individuals were born at full term (61 out of 68, or 89.7%), had average birth weight (62 out of 68, or 91.2%), were fed with bottles (29 out of 68, or 42.6%), and had parents who were consanguineous (52 out of 68, or 76.5%). The primary factors contributing to hypocalcemia in this study were vitamin D deficiency (19/68) (27.9%) and hypoparathyroidism (18/68) (26.5%). The predominant manifestations of hypocalcemia observed in these individuals were seizures (54/68) (79.4%) and stridor (54/68) (79.4%). The presence of carpopedal spasms and bone pain as indicators of hypocalcemia showed a strong correlation with the patient's age group. Additionally, bone pain was found to have a significant link with the causes of hypocalcemia in this study. Congenital vitamin D deficiency and transitory hypoparathyroidism primarily manifest during the newborn and infancy stages, whereas other causes predominantly occur during the early and later stages of childhood. Rachitic alterations predominantly manifest in the age range of 1 to 5 years, accounting for 16 out of 25 cases (57.1%). The typical age range for the onset of hypocalcemia in patients is between 1 and 5 years old. The primary etiology of hypocalcemia observed in this study was attributed to a deficit in vitamin D. The prevailing clinical manifestations in these patients were seizures and stridor.

Keywords: Pediatric Hypocalcemia, Patients, Consanguineous, Etiology, Deficiency.

INTRODUCTION

Hypocalcaemia is a condition characterised by a total serum calcium concentration below 2.1 mmol/L (8.5 mg/dL) in neonates, a lower level in term infants, and a lower level in preterm infants. Calcium is the most abundant mineral in the body, with 99% of the total calcium content stored in bone and the remaining 1% distributed throughout the extracellular fluid (Jefferies, C. and Gavin, R. 2007: Gertner, J. M. 1990). The plasma-ionized calcium fraction is biologically active and tightly controlled. The extracellular calcium concentration is regulated by the Ca-sensing receptor (CaSR), parathyroid hormone (PTH), and vitamin D. PTH induces bone mineral release, increasing circulating calcium and phosphate concentrations. In the kidney, PTH increases renal tubular calcium reabsorption and excretion and stimulates the conversion of vitamin D into its active form, 1,25-dihydroxyvitamin D (Singh, J. *et al.*, 2003).

Calcium is the most prevalent mineral in the human body, with 99% of its total concentration stored in bone tissue and less than 1% present in the serum. Calcium is primarily present in the form of hydroxyapatite crystals within the skeleton, with 50% in circulation in the free ionised form, 40% bound to protein, and 10% complexed with anions. The plasma ionised calcium fraction is biologically active and subject to strict regulation. The extracellular calcium concentration is regulated by the Ca-sensing receptor (CaSR), parathyroid hormone (PTH), and vitamin D. PTH affects the bone and kidney, increasing calcium and phosphate concentrations and stimulating the conversion of vitamin D into its active form (Favus, M. J. 2006; Lifshitz, F. 2007).

Hypocalcemia is a condition characterized by low calcium levels, causing central nervous system irritability and poor muscular contractility. This

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leads to various peripheral and CNS effects, including paresthesias, tetany, seizures, and psychiatric changes in children. Cardiac function may also be impaired due to poor muscle contractility. Common causes include abrupt discontinuation of placental calcium supply at birth, limited or no dietary calcium, transient increased serum PTH concentration, end-organ resistance to PTH and 1,25 (OH)2D, and elevated serum CT concentration. Hypocalcemia may also occur in patients with intrauterine growth retardation or infants of mothers with insulin-dependent diabetes (Sarkar, S. *et al.,* 2003; Taylor, S. C. *et al.,* 2003; Crook, M. A. *et al.,* 2001; Wasant, P. *et al.,* 2002). Hypoparathyroidism in infants is a complex condition characterized by a variety of genetic disorders. It can occur sporadically or with different inheritance modes. Defective parathyroid hormone (PTH) can be inherited in autosomal-dominant or autosomal-recessive forms, with the latter often leading to embryonic dysgenesis. Chromosome 22q11.2 deletion can cause various phenotypic manifestations, including Digeorge and velocardiofacial/Shprintzen syndromes (Sarici, S. U. *et al.,* 2004; Rubin, L. P. 1998). Dysregulation of PTH can result from a mutation of CaR, leading to hypocalcemia with hypercalciuria. Chronic hypomagnesemia can cause impaired end-organ response to PTH, while maternal anticonvulsant therapy may result in neonatal hypocalcemia. Severe deficiency can lead to disturbed blood biochemistries, known as "the refeeding syndrome" or "hungry bone syndrome." Mitochondrial fatty acid disorders can cause metabolic anomalies and organ dysfunction (Venkataraman, P. S. *et al.,* 1987).

PATIENT AND METHOD

An observational study was conducted from April 1, 2017, to April 30, 2018, at the Children's Welfare Teaching Hospital. The study included 68 children who arrived with symptomatic hypocalcemia and were admitted to the medical wards.

The age of the patients spanned from infancy to 15 years.

All patients were admitted to separate wards of the Children Welfare Teaching Hospital as cases of newly diagnosed symptomatic hypocalcemia.

The initial data is obtained using a questionnaire administered to the primary caregiver of the patient, typically the mother.

The data we collected included information on age, sex, gestational age, birth weight, consanguinity, feeding method, family history of the same problem, signs and symptoms, dietary history, related illnesses, and anomalies, as well as a comprehensive physical examination that assessed for indicators of hypocalcemia and rickets.

The investigations encompassed a comprehensive assessment of all patients, including measurements of total serum calcium, phosphorus, ALP, blood urea, serum creatinine, serum PTH, serum vitamin D, serum magnesium, and serum albumin. Additionally, an abdominal ultrasound was performed.

A blood sample was obtained by a highly skilled technician, who took care to avoid applying pressure and used a liquid-color photometric test.

The accepted range for serum calcium is typically 8.5-10.5 mg/dl, serum phosphorus is 2.7-4.5 mg/dl, serum 25-hydroxy vitamin D (25 (OH)D) is 30-100 ng/ml, and PTH is 8-65 pg/ml.

We provide 24-hour collection services for calcium and phosphorus, as well as X-rays for the wrist, head, and chest, as well as MRI and CT scans based on individual requirements.

The examinations and radiological studies were conducted at the laboratory and radiological facility of the medical city.

A comprehensive follow-up is conducted on all patients within a period of less than one year in order to determine the temporary character of some disorders, such as transient hypoparathyroidism and vitamin D deficiency. This follow-up is carried out at the endocrinological outpatient clinic in the Children's Welfare Teaching Hospital.

Congenital vitamin D deficiency can be identified by evaluating the vitamin D levels in both the neonate or infant and their mother.

Exclusion was applied to cases in the following situations: 1- Any patients who were lost after the first diagnosis (20 patients) and started emergency therapy without completing their lab investigation.

2- Five neonatal patients were discharged from the hospital before completing their laboratory investigations and receiving a final diagnosis due to their family duties.

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The purpose of the study was to investigate the primary causes of hypocalcemia in different age groups, as well as to examine the most prevalent signs and symptoms associated with each cause of hypocalcemia.

RESULTS

The patients were classified into four age groups based on their age at presentation: those aged less than or equal to 1 month, 1-12 months, 1-5 years (the most prevalent age group, comprising 28 out of 68 patients, or 41.2% of the total), and those aged more than or equal to 5 years. The majority of the patients, 61 out of 68 (89.7%), were born at full term and had an average birth weight of 62 out of 68 (91.2%). Additionally, most of the patients, 52 out of 68 (76.5%), were the outcome of positive consanguineous marriage. Out of the total patients, 29 (42.1%) were fed with a bottle, while 25 (36.8%) were exclusively breastfed.

Table 1: classification of age group

		No.	%
Age at presentation	≤ 1 m	5	7.4
	1 -12 months	10	14.7
	1-5 y	28	41.1
	>5 y	25	36.8
Gestational age	Full term	61	89.7%
	Preterm	7	10.3%
Birth Weight category/Kg	<2.5	5	7.4%
	2.5-4	62	91.2%
	>4	1	1.5%
Consanguinity	Negative	16	23.5%
	Positive	52	76.5%
Type of feeding	Bottle	29	42.6%
	Breast	25	36.8%
	Mixed	14	20.6%

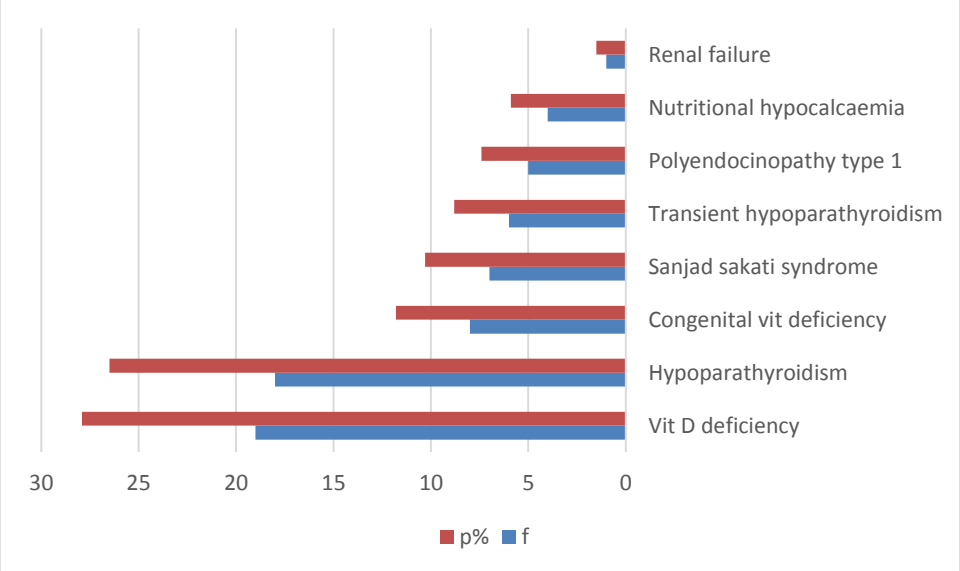

Fig 1: Distribution of patients with hypocalcaemia according to etiological factors

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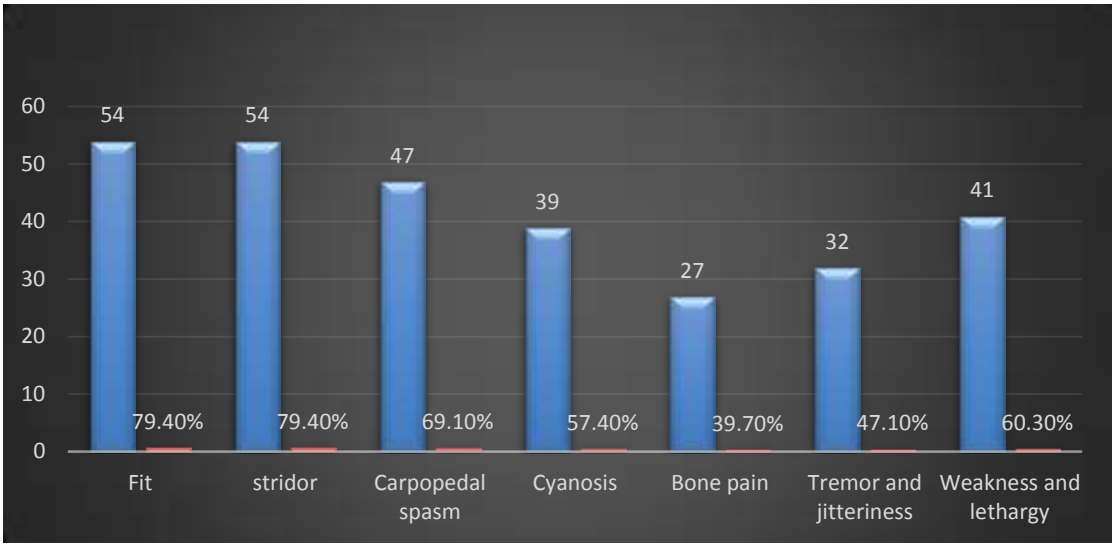

Fig 2: Distribution of patients according to frequency of signs and symptoms

Table 2: Association of frequency of signs and symptoms and age groups of the patients

Age category									**P-value**
	≤ 1 m (n=5)		1-12 m (n=10)		1-5 y (n=28)		≥5 y (n=25)		
	No	%	No	%	NO	%	No	%	
Fit (n=54)	5	100.0%	9	90.0%	22	78.6%	18	72.0%	0.4
Stridor (laryngospasm) (n=54)	5	100.0%	8	80.0%	21	75.0%	20	80.0%	0.6
Carpopedal spasm (n=49)	0	00.0%	6	60.0%	18	64.3%	23	92.0%	0.02
Cyanosis (n=39)	4	80.0%	6	60.0%	17	60.7%	12	48.0%	0.5
Bone pain (n=27)	0	0.0%	0	0.0%	7	25.0%	20	80.0%	0.01
Tremor and jitteriness (n=32)	3	60.0%	6	60.0%	11	39.3%	12	48.0%	0.6
Weakness and lethargy (n=41)	2	40.0%	5	50.0%	14	50.0%	20	80.0%	0.08

Table 3: The association between age groups and the final diagnosis

causes	**Age group**							
	≤1month		1-12months		1-5years		≥5years	
	No.	%	No.	%	No.	%	No.	%
Vitamin D deficiency (19)	0	0	0	0	13	68.4	6	31.6
Hypoparathyroidism (18)	0	0	0	0	2	11.1	16	88.9
Congenital vitamin D deficiency (8)	2	25	6	75	0	0	0	0
Sanjad Sakati syndrome (7)	0	0	1	14.3	6	85.7	0	0
Transient hypoparathyroidism (6)	3	50	3	50	0	0	0	0
Polyendocrinopathy type 1 (5)	0	0	0	0	3	60	2	40
Nutritional hypocalcemia (4)	0	0	0	0	4	100	0	0
Renal failure	0	0	0	0	0	0	1	100

Table 4: Association between rachitic changes and age categories of the studied group

Age category	**Rachitic changes**				**P-value**
	Yes		No		
	No.	%	No.	%	
< 1 m	1	20.0%	4	80.0%	**0.01**
1 m-1 year	4	40.0%	6	60.0%	
1-5 y	16	57.1%	12	42.9%	
>5 y	4	16.0%	21	84.0%	

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Table 5: Elements of polyendocrinopathy in addition to hypoparathyroidism

Associated anomalies	Frequency (5)	Percent
Addison disease	4	80
candidiasis	4	80
alopecia	2	40

DISCUSSION

Hypocalcemia is a prevalent phenomenon in the context of patient care, with the majority of cases occurring in individuals aged 1-5 years (41.2%) and above five years (36.8%) who have been diagnosed with vitamin D deficiency. This finding is consistent with those of previous studies. Congenital vitamin D deficiency is most prevalent during the early infantile period, specifically between the ages of 32 and 121 days. Furthermore, premature children are more likely to be diagnosed with vitamin D deficiency (6/7), indicating a high prevalence of moderately severe vitamin D deficiency in Arabic preterm infants.

The study revealed that there were no statistically significant differences in gestational age and birth weight between the various causes of hypocalcemia, including vitamin D deficiency and transient hypoparathyroidism. The prevalence of consanguinity was 76.5% among the patient cohort, with the majority of cases of polyendocrinopathy and Sanjad Sakati syndrome occurring in individuals with a positive family history of consanguinity. It has been demonstrated that primary immune deficiency is prevalent in populations with high rates of consanguinity. Furthermore, a positive consanguinity rate was identified in the majority of cases involving vitamin D deficiency and hypoparathyroidism (Thomas, T. C. *et al.*, 2012; Jackson, G. L. *et al.*, 2003; AliZadeh-Taheri, P. *et al.*, 2013). The majority of patients who were exclusively breastfed were diagnosed with vitamin D deficiency and congenital vitamin D deficiency as the underlying causes of symptomatic hypocalcemia.

The study revealed that vitamin D deficiency was the most prevalent diagnosis, followed by hypoparathyroidism and congenital vitamin D deficiency. The most common presentation of hypocalcemia in neonatal patients was lethargy and laryngospasm, followed by cyanosis, tremor, jitteriness, and weakness. In the age group between 1 and 12 months, the most common clinical presentation was a fit, with congenital vitamin D deficiency being the most common underlying cause. In early childhood, the most common presentation was a fit, with 78.6% of patients (Tenhola, S. *et al.*, 2016; Meada, S. S. *et al.*, 2006) experiencing an afebrile fit. In patients aged five and over, the most common presentation was a carpopedal spasm, followed by laryngospasm, with hypoparathyroidism being the most common underlying cause (Sheth, D. P. *et al.*, 1997; Khan, M. A. *et al.*, 2018; Shoback, D. M. *et al.*, 2016; Al Faraj, S. A. & Almutairi, K. 2003).

The study revealed that age group categories exert a negligible influence on the signs and symptoms of hypocalcemia, with the exception of bone pain and carpopedal spasm. This finding is consistent with those of previous studies conducted in Saudi Arabia and elsewhere, which have demonstrated that bone pain and low back pain are more prevalent in late childhood and adolescent patients with hypocalcemia. Patients with congenital vitamin D deficiency presented with fatigue (75%), tremors and jitteriness (62.5%), lethargy and weakness (62.5%), laryngospasm (50%), and cyanosis (37.5%). The most common presenting symptoms of hypoparathyroidism were carpopedal spasm (88.9%), followed by laryngospasm (stridor) (77.8%), and fit (72.2%). In patients with nutritional hypocalcemia, the most common presentations were laryngospasm and carpopedal spasm (100%), followed by bone pain and, lethargy and weakness (75% of patients).

The study revealed that patients with polyendocrinopathy type 1 frequently present with a constellation of symptoms, including bone pain, lethargy, weakness, fits, and carpopedal spasms, laryngospasm, and cyanosis, tremor, and jitteriness. This finding is consistent with those of previous studies, which identified clumsiness, muscle cramps, grand mal seizures, laryngospasm, and hypotension as common symptoms (Narchi, H. *et al.*, 2000). Only one patient presented with renal failure and hypocalcemia, while all patients with Sanjad Sakati syndrome presented with tetany. The most prevalent deficiency was vitamin D, which was observed in patients exhibiting laryngospasm, fits, carpopedal spasms, lethargy, weakness, and cyanosis. Furthermore, the study revealed that bone pain represents the most significant factor in hypocalcemia presentations, potentially attributable to the fact that older

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children exhibit a greater number of hypocalcemia-related symptoms.

The study revealed that the most prevalent age group for symptomatic hypocalcemia and vitamin D deficiency was between 1 and 5 years old, followed by those aged five years and above. The most common presentation of hypoparathyroidism was in patients aged five years and older, which is consistent with the findings of previous studies. The age at which congenital vitamin D deficiency was most commonly presented was between one and 12 months, while Sanjad Sakati syndrome was most frequently diagnosed between one and five years of age. The majority of cases of transient hypoparathyroidism occurred in patients less than or equal to one month old and between one and 12 months old, with a 50% incidence rate. The age at presentation of hypocalcemia in patients with polyendocrinopathy type 1 was most frequently observed to be between 1 and 5 years old and in individuals older than or equal to 5 years old. The occurrence of nutritional hypocalcemia was most prevalent in children younger than three years of age. Additionally, the study identified that the most prevalent immunological anomalies were Addison disease and chronic mucocutaneous candidiasis, observed in 80% of patients, while alopecia was present in 40% of cases.

CONCLUSION

The evidence presented in this study suggests that where the age at presentation of patients with hypocalcemia is most frequently between one and five years. The majority of these patients were full-term and average weight, with consanguineous parents.

The most common cause of hypocalcemia in this study was vitamin D deficiency, and the most common presenting signs and symptoms were lethargy and laryngospasm.

The majority of cases of rachitic changes in this study occurred between the ages of one and five years.

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