Original article

Characterization of a cohort of patients with hypercalcemia in a tertiary pediatric hospital

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ABSTRACT

Introduction. Hypercalcemia is infrequent in pediatrics, of diverse etiology, and with multiorgan morbidity.

Objective. Describe the etiology, biochemistry, clinical, and treatment in pediatric patients with hypercalcemia.

Population and methods. Retrospective and descriptive study of a cohort of patients with hypercalcemia between 2008 and 2022. They were classified into three groups (G): hypercalcemia of iatrogenic cause (G1), parathyroid hormone (PTH) independent (G2), or PTH-dependent (G3).

Results. One hundred forty-seven patients were included; 57% were male, with a median age of 3.7 years, median calcemia of 11.8 mg/dl, and mean phosphatemia of 4.9 mg/dl. Symptoms were present in 29% of patients, and 28.6% required additional treatments to those of the first line.

In G1, 76 patients (51.7%) were included; in G2, 58 (39.4%), and in G3, 13 (8.8%).

Median calcemia was lower in G1 vs. G2 and G3 (11.6 mg/dl, 12.6 mg/dl, and 12.3 mg/dl), and mean phosphatemia was lower in G3 vs. G1 and G2 (3.7 mg/dl, 5.3 mg/dl, and 4.9 mg/dl).

Most of the patients with hypercalcemia were asymptomatic and did not require additional treatments. The percentage of symptomatic patients and the percentage requiring additional treatment were lower in G1 than in the other two groups.

Conclusions. Iatrogenesis was the most frequent cause, presenting lower calcemia, while PTH-dependent causes presented the lowest phosphatemia. PTH-independent causes represented a diagnostic and therapeutic challenge due to lacking a characteristic biochemical profile.

Keywords: hypercalcemia; pediatrics; iatrogenic disease; parathyroid hormone; calcium metabolism disorders.

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INTRODUCTION

Hypercalcemia is an uncommon condition in pediatrics that can be caused by different pathophysiological mechanisms, such as increased gastrointestinal absorption of calcium, decreased renal excretion, increased bone resorption, or combined mechanisms.[1,2]

The underlying etiologies may be congenital or acquired and should be diagnosed early to initiate appropriate treatment.[3] Although the most frequent causes in the adult population are hyperparathyroidism and oncologic diseases,[2,3] scarce information is available about children.

In pediatrics, hypercalcemia is generally asymptomatic,[2,4] however, it can become a medical emergency in the acute form, and generate irreversible renal damage in the chronic form, increasing the patient's morbidity and mortality.[5]

Our study aimed to describe the etiologies, biochemical profiles, clinical characteristics, and treatment of pediatric patients with hypercalcemia treated in a tertiary pediatric center.

POPULATION AND METHODS

A retrospective and descriptive study of medical records with a recorded diagnosis of hypercalcemia in patients under 18 years of age attended at the Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan between 2008 and 2022 was carried out. Outpatients and/or hospitalized patients with hypercalcemia as a reason for consultation/admission or a laboratory finding were included.

Hypercalcemia was defined as an increase in serum calcium level greater than two standard deviations (SD) for the reference values according to age, confirmed with at least a second sample. Mild hypercalcemia was considered when serum calcium was >10.5 mg/dl and ≤12 mg/dl; moderate >12 mg/dl and ≤14 mg/dl; and severe >14 mg/dl, according to the classification used in the international literature.[1,5,6]

The following data were analyzed:
a) **Demographics**: Age and sex.
b) **Biochemical**: Calcemia corrected by albumin (the highest value was recorded), phosphatemia, parathormone (PTH), 25-(OH)-vitamin D, and renal function (glomerular filtration rate).
c) **Clinical**: Symptomatic patients were defined as those who had at least one symptom and sign related to hypercalcemia, such as cardiovascular symptoms and signs (arterial hypertension, compatible ECG abnormalities), gastrointestinal (nausea, vomiting, anorexia, constipation, abdominal pain, pancreatitis), neuromuscular (headaches, seizures, impaired sensorium), renal (polyuria, polydipsia, dehydration, decreased glomerular filtration rate, nephrocalcinosis), asthenia, adynamia, or poor postnatal growth.
d) **Therapeutics**: First-line treatment was defined as reducing hypercalcemic agents, such as dairy products, parenteral nutrition and drugs (vitamin D and its analogs, calcium salts, hydrochlorothiazide, retinoic acid), and hyperhydration (with or without furosemide); additional treatments were defined as the use of corticoids, pamidronate, calcitonin, cinacalcet, and parathyroid surgery or tumor resection.

When faced with a pediatric patient with hypercalcemia in our center, we used an algorithm for its diagnosis, presented in *Figure 1*. Accordingly, patients were classified into three groups (G): hypercalcemia of iatrogenic cause (G1), PTH-independent (G2), or PTH-dependent (G3), according to the primary pathophysiological mechanism.

Iatrogenic hypercalcemia (G1) was defined as hypercalcemia caused as an unavoidable and unintended side effect of the use of hypercalcemic agents aimed to improve the patient's underlying pathology and which responded favorably to their reduction or discontinuation, regardless of the PTH value. This group was subclassified into G1a patients with chronic kidney disease (CKD) due to decreased glomerular filtration rate ≤50 ml/minute/1.73 m^2 and G1b patients without glomerular filtration rate compromise.

PTH-independent hypercalcemia (G2) was defined as having plasma PTH values ≤20 pg/ml, and PTH-dependent hypercalcemia (G3) that caused by elevated PTH levels >20 pg/ml. In G2 and G3, patients were subclassified according to the underlying etiology.

G2 was subclassified into G2a: oncologic cause (hypercalcemia occurring at the debut or relapse of an oncologic disease), G2b: granulomatous cause (hypercalcemia caused by disseminated granulomatous disease, infectious or not) and G2c: genetic cause (hypercalcemia associated with isolated genetic syndromes or entities).

G3 is subclassified into G3a: primary hyperparathyroidism (hypercalcemia associated with PTH synthesis in patients without CKD) and G3b: tertiary hyperparathyroidism (hypercalcemia

associated with PTH synthesis in patients with CKD).

The research protocol was presented to the Hospital Garrahan Research Committee, which approved it in April 2021. Informed consent was not required.

Statistical analysis

Continuous variables were expressed as mean, SD, median, and interquartile range (IQ). Categorical variables were expressed as proportions or percentages. The ANOVA multiple comparisons and Kruskal-Wallis tests were used for quantitative data with normal and non-normal distributions, respectively. For categorical data, the test for comparison of proportions and Fisher's exact test were used.

Statistical analysis was performed with Statistix 7Ô (Analytical Software, Tallahassee, FL, USA).

RESULTS

We reviewed 165 medical records of patients diagnosed with hypercalcemia and included 147 patients (*Figure 2*), predominantly male sex, median age of 3.7 years, median calcemia 11.8 mg/dl, and mean phosphatemia 4.9 mg/dl. Symptoms were present in 29% of patients, and 28.6% required additional treatments (*Table 1*).

The etiologies of the different subgroups are presented in *Table 2.*

In the comparative analysis of the subgroups (*Table 3*), G1a patients had a higher median age than G1b patients, a lower percentage of symptomatic patients, and a lower requirement for additional treatments, respectively.

Within G1a, 35/45 patients were tested for 25-OH-vitamin D: 5 had <20 ng/ml; 10 had between 20 ng/ml and 30 ng/ml; and 20 had >30 ng/ml (maximum of 57.9 ng/ml). Within G1b, 20/31 patients were analyzed: 9 patients had <20 ng/ml; 1, between 20 ng/ml and 30 ng/ml; and 10 had >30 ng/ml (maximum of 69.7 ng/ml). No patient had 25-OH-vitamin D in the toxicity range.

As expected, G2c patients had a lower median age than G2a and G2b. G2a patients were the most symptomatic compared to G2b and G2c; the most frequent etiologies were rhabdomyosarcoma and rhabdoid tumor, both with bone metastases. Six of twenty-one oncologic patients died within one month of the diagnosis of hypercalcemia, and three others only managed to normalize calcemia after tumor removal (ovarian dysgerminoma, hemangioendothelioma, mesoblastic nephroma). Although the requirement for additional treatments was similar in the three G2 subgroups, pamidronate was more commonly used in G2a (33%) and corticosteroid in G2b (28%).

The median PTH of G3b was significantly higher than that of G3a and higher than that of G1a. In turn, in patients with CKD, the mean phosphatemia was higher in G3b vs. G3a.

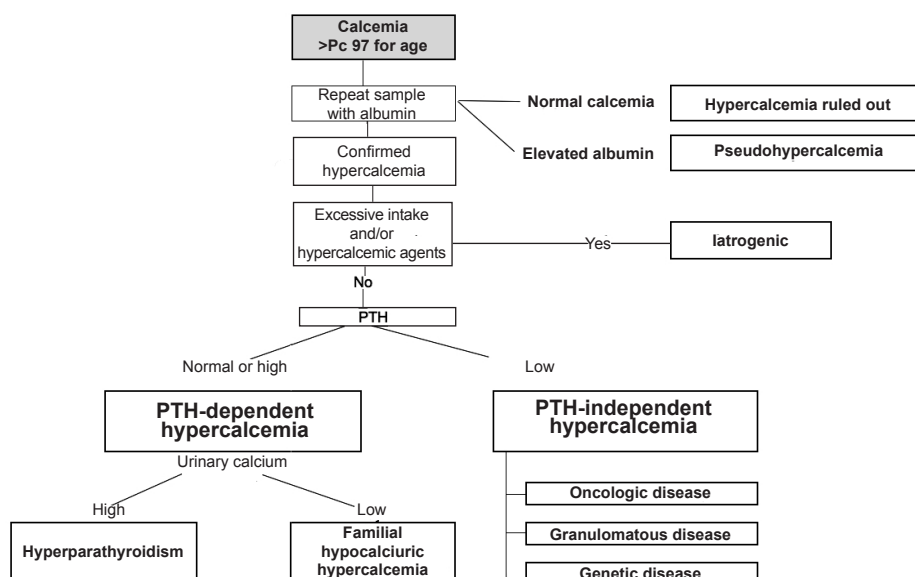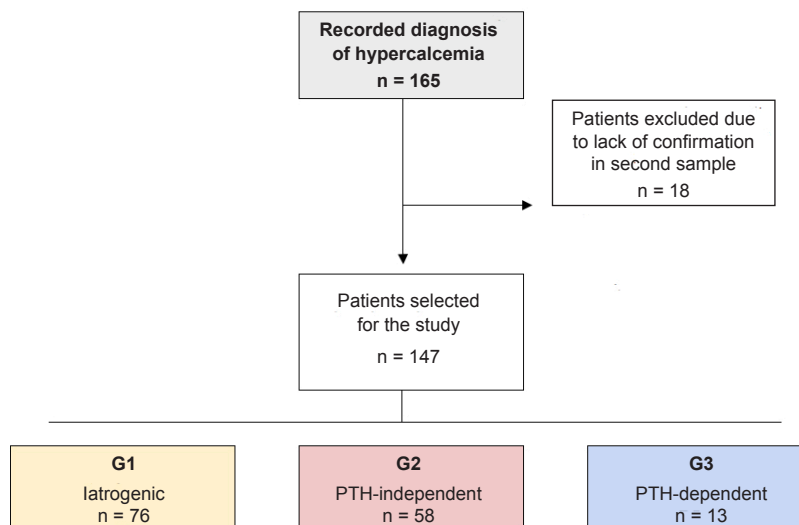FIGURE 1. Diagnostic algorithm for pediatric hypercalcemia

FIGURE 2. Patient flow

Four out of seven patients in G3a had symptoms of hypercalcemia, whereas in G3b, all patients were asymptomatic. All patients in G3b had skeletal signs of chronic hyperparathyroidism, whereas in G3a, only two out of seven had them.

Treatment of primary hyperparathyroidism consisted of surgical resection in the three patients with adenoma and cinacalcet in one patient with familial hypocalciuric hypercalcemia; the remaining three required only first-line measures. Treatment of patients with tertiary hyperparathyroidism consisted of subtotal parathyroidectomy in four of six; another patient improved with first-line measures, and one died of complications of CKD.

DISCUSSION

This is one of the first studies describing an extensive pediatric sample of 147 patients with hypercalcemia in a single third-level center.

As reported in the literature, hypercalcemia was asymptomatic in 103/147 patients (70%) and did not require other therapeutic measures in addition to first-line treatment in 71.4%.

Our results showed that the iatrogenic cause (G1) was the most frequent. In this group of patients, hypercalcemia was mild (11.6 mg/dl); therefore, they had fewer symptoms and additional treatment requirements.

The pathophysiologic mechanism most frequently involved in patients with iatrogenic causes of hypercalcemia is the increased

TABLE 1. Clinical, biochemical and therapeutic characteristics of the total sample and of the iatrogenic cause (G1), parathormone-independent (G2) and parathormone-dependent (G3) groups

Groups	Total	G1	G2	G3
Patients (number)	147	76	58	13
Sex (n, males/females)	84/63	43/33	33/25	8/5
Age (years) median (IQ)	3.7 (0.8-10.5)	3.3 (0.8-11.7)	2.9 (0.7-9.5)	9.9 (3.9-13)
Calcemia[1] (mg/dl) median (IQ)	11.8 (11.2-13.5)	11.6 (11.1-12.5)	12.6 (11.3-14.8)	12.3 (11.5-13.8)
Phosphatemia[2] (mg/dl) mean (DE)	4.9 (1.7)	5.3 (1.7)	4.9 (1.6)	3.7 (1.96)
Symptomatic patients[3]	44/147	10/76	29/58	5/13
Additional treatments[4]	42/147	8/76	26/58	8/13

[1]Kruskal-Wallis p <0.05; Bonferroni (G1 vs. G2); [2] ANOVA p <0.02; Bonferroni (G3 vs. G1); [3] p <0.04 (G1 vs. G2 and G3); [4] p <0.01 (G1 vs. G2 and G3).

IQ: interquartile range. SD: standard deviation.

gastrointestinal absorption of calcium. In this regard, it is essential to remember that the recommended daily calcium intake is standardized for healthy children and adolescents. This situation is very different from that of sick patients, whose requirements may vary according to immobilization, delayed growth and development, dehydration, altered renal function, 25-OH-vitamin D status, and other mechanisms that increase susceptibility to hypercalcemia. On the other hand, in patients with chronic diseases, inadequate adherence to treatment can lead to difficulties in adjusting doses.

Patients with CKD reported the fewest symptoms, which could be attributed to the chronicity of metabolic changes in this population.

In oncologic patients (G2a), hypercalcemia was moderate to severe (13.7 mg/dl) and frequently symptomatic, being associated with an ominous prognosis in 6/21, 30% of cases. The mechanisms involved in this group are multiple: excess inflammatory cytokines, bone metastases, and increased calcitriol synthesis due to the deregulated activity of tumor 1-alpha-hydroxylase and/or PTHrp (PTH-related protein) synthesis.[1,5] These mechanisms mainly

TABLE 2. Classification of patients according to the different groups: iatrogenic cause (G1), parathormone independent (G2), and parathormone dependent (G3) and the underlying etiologies in the G2 and G3 subgroups

G1 IATROGENIC CAUSE (n 76)	G1a with CKD (n 45) G1b without CKD (n 31)	
G2 PTH INDEPENDENT (n 58)	G2a oncologic cause (n 21)	*Rhabdomyosarcoma with metastasis (MTS) (n 4) *Rhabdoid tumor with MTS (n 3) *Acute lymphoblastic leukemia (n 3) *Hepatoblastoma (n 3) *Lymphoma (n 2) *Ovarian dysgerminoma (n 2) *Fibrosarcoma (n 1) *Mesoblastic nephroma (n 1) *Hemangioendothelioma (n 1) *Medulloblastoma (n 1)
	G2b granulomatous cause (n 21)	*Infections (n 18) -*Candida* (n 6) -*Aspergillus* (n 4) -tuberculosis (n 4) -*Staphylococcus* (n 2) -toxoplasmosis (n 1) -multifactorial (n 1) *Subcutaneous fat necrosis (n 3)
	G2c genetic cause (n 16)	*Syndromic (n 11) -Williams syndrome (n 6) -Mc Cune Albright with neonatal Cushing (n 2) -Adrenoleukodystrophy with adrenal insufficiency (n 1) -Hypophosphatasia (n 1) -Indeterminate genetic syndrome (n 1) *Idiopathic infantile hypercalcemia (n 5)
G3 PTH DEPENDENT (n 13)	G3a primary hyperparathyroidism (n 7)	*Parathyroid adenoma (n 3) *Familial hypocalciuric hypercalcemia (n 3) *Transient neonatal hyperparathyroidism (n 1)
	G3b tertiary hyperparathyroidism (n 6)	

PTH: parathyroid hormone. CKD: chronic kidney disease with decreased glomerular filtration rate <50 ml/minute/1.73 m^2.

Table 3. Comparative analyses of subgroups

Variables	G1 Iatrogenic			G2 PTH-independent				G3 PTH-dependent		
	G1a with CKD	G1b without CKD	*p*	G2 oncologic	G2 granulomatous	G2 genetic	*p*	G3a primary	G3b tertiary	*p*
Patient (years)	45	31		21	21	16		7	6	
Age (years) Median (IQ)	7.2 (1.7-13.5)	2.4 (0.3-6.7)	<0.01	5.7 (1.1-11.5)	5.4 (0.6-10.2)	0.8 (0.45-1.15)	<0.01 A	10 (5.2-15.2)	8,9 (2.7-11.7)	ns
Calcemia (mg/dl) Median (IQ)	11.5 (11.2-12.2)	11.7 (11-13.9)	ns	13.9 (11.6-15.5)	12.6 (11.7-14.2)	11.3 (10.9-16.1)	ns	13.8 (11.4-13.9)	12.1 (11.5-12.5)	ns
Phosphatemia (mg/dl) Mean (SD)	5.2 (1.7)	5.2 (1.5)	ns	4.7 (1.9)	5.2 (1.6)	4.9 (1,2)	ns	2.4 (1)	5.3 (1.5)	<0.01
PTH (pg/ml) Median (IQ)	101 (48-267)	<20*	<0.01	<20*	<20*	<20*	ns	62.7 (44-1.349)	2.299 (1.556-3.554)	<0.02
Symptomatic patients n (%)	1 (3)	9 (29)	<0.01	16 (76)	6 (28)	7 (43)	<0.03 B	4 (57)	0	
Additional treatments n (%)	2 (4)	6 (19)	<0.01	12 (57)	8 (38)	6 (38)	ns	4 (57)	4 (66)	ns

CKD: chronic kidney disease with decreased glomerular filtration rate <50 ml/minute/1.73 m².

* PTH measurements available on G1b (n 21), G2a (n 12), G2b (n 15), G2c (n 12).

ns: not significant. IQ: interquartile range. SD: standard deviation.

A: G2c vs. G2a and G2b. B: G2a vs. G2b and G2c.

produce increased bone resorption, so patients frequently require additional treatments, such as pamidronate and/or tumor removal.

Hypercalcemia secondary to granulomatous disease (G2b) is caused by deregulated calcitriol synthesis in the granuloma,[1,7] resulting in increased intestinal calcium absorption. In our study, infectious etiology was the most frequent (*Candida*, *Aspergillus,* and tuberculosis), followed by fat subcutaneous necrosis of the newborn.[8]

Among the genetic (G2c) independent causes of PTH, hypercalcemia in neonatal Cushing's syndrome occurs due to increased bone resorption; in primary adrenal insufficiency, by hemoconcentration;[1] and in Williams syndrome, by increased gastrointestinal calcium absorption.[2,3,7,9]

In agreement with what has been published, non-syndromic genetic PTH-independent causes, previously known as idiopathic hypercalcemia of infancy, were very infrequent (5/147; 3.4%). The mechanism involved in this entity is the increased gastrointestinal absorption of calcium mediated by an increase in calcitriol, either by stimulation of its synthesis by the renal loss of phosphate (mutations of the sodium-phosphorus cotransporter or its cofactor) or by the decrease in its degradation (mutations of the enzyme 24-hydroxylase that converts it to an inactive metabolite).[10,11]

In contrast to the adult population, PTH-dependent causes (G3) were infrequent in our population (13/147; 8.9%). In this group, although calcemia values did not indicate the underlying etiology (primary vs. tertiary), the low phosphatemia values suggested the diagnosis of primary hyperparathyroidism. The higher phosphatemia in tertiary hyperparathyroidism is evidence of resistance to the phosphaturic action of PTH in patients with compromised glomerular filtration rates. In turn, this latter group had significantly higher PTH levels, which can be differentiated from patients with primary hyperparathyroidism (G3a) and patients with iatrogenic causes and CKD (G1a).

The finding of a parathyroid adenoma in pediatrics is infrequent and should lead to the suspicion of a predisposing genetic cause.[12] In our case report, one of the patients had tuberous sclerosis as the underlying disease; only two cases have been reported in pediatric patients.[13,14]

In the three patients with familial hypocalciuric hypercalcemia, the presence of inactivating variants of the calcium-sensing receptor (CaSR) in

a heterozygous state was confirmed by molecular study. This results in decreased sensitivity of parathyroid and renal cells to calcemia.[7,10]

Transient hyperparathyroidism can occur in neonates due to maternal hypocalcemia during pregnancy.[7,10] Hence, it is essential to emphasize that the mother should always request a phosphocalcic profile in case of PTH-dependent hypercalcemia in the newborn.

One limitation of our study is that the selection of patients was retrospective, based on the diagnosis of hypercalcemia recorded in the clinical history and not on laboratory determinations. This could have led to underreporting, mainly of patients with iatrogenic causes.

According to previous publications,[2-5,15] periodic calcemia controls should be performed in patients with risk factors, such as hypercalcemic agents, immobilization, oncologic, granulomatous or predisposing genetic disease. In case of moderate-severe and symptomatic hypercalcemia, it is suggested to hospitalize the patient, immediately suspend all hypercalcemic agents (including dairy products, formulas, and parenteral nutrition with calcium and drugs), evaluate the rest of the internal environment, and start hyperhydration early, associated with furosemide once normohydration has been achieved. In patients with CKD receiving renal replacement therapy, dialysis should be optimized.

In the absence of an adequate response to first-line treatment, a consultation with an endocrinologist is suggested to consider additional treatment.[5]

CONCLUSIONS

In this cohort, most of the patients with hypercalcemia were asymptomatic and did not require additional treatments to the first-line ones. Iatrogenic was the most frequent cause, presenting with lower calcemia. Primary PTH-dependent causes presented the lowest phosphatemia. PTH-independent causes represented a diagnostic and therapeutic challenge due to the lack of a characteristic biochemical profile and the heterogeneity and severity of the etiologies involved. ■

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