

HYPERCALCEMIA IN CHILDREN

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ABSTRACT

Hypercalcemia is less common in children than in adults, but is more likely to be clinically significant in younger patients as routine biochemical screening tests are rarely performed in children. The serum calcium levels are maintained through the interplay of parathyroid, renal, and skeletal factors. The most common causes of hypercalcemia are primary (hyperparathyroidism or cancer) but a variety of unusual etiologies must be considered in children. The initial approach to the medical treatment of severe or symptomatic hypercalcemia is to increase the urinary excretion of calcium. In most cases, hypercalcemia is due osteoclastic bone resorption, and the effective treatment is based on agents that inhibit or destroy osteoclasts. Parathyroid surgery is recommended for all children with primary hyperparathyroidism.

Keywords: hypercalcemia, pediatrics, parathyroid

Hypercalcemia is not a common pediatric problem; the actual incidence in children is unknown, although it is less common than in adults. In adults, hypercalcemia is the primary malignancy-associated endocrine/electrolyte disorder; it is present in 5% of all malignancies, or in 15 per 100,000 total patients [1]. The normal values of blood calcium in children varies from 8.5 to 10.3 mg%. Hypercalcemia is considered, depending on age, at the following values: premature -> 9 mg%, term newborn -> 10, 4 mg%, child / adolescent -> 10.4 mg%. Most of the body calcium (98% is in the skeleton and only 2% is in circulation; half of this one is free calcium (ionized) Ca⁺⁺, physiologically active. 1% is fastened to the rest of the serum proteins. Calcium absorption and regulation involve a complex interplay between multiple organ systems and

regulatory hormones [2]. The three predominant sources of calcium and targets for regulation are the bones, renal filtration and reabsorption, and intestinal absorption. The major regulators of calcium levels are parathyroid hormone (PTH) and vitamin D, which target the bones, intestine, and kidney to increase serum calcium. Calcitonin, a more minor player in regulation, decreases serum calcium by its effects on bone and kidney.

Etiology

Hypercalcemia is caused by either primary hyperparathyroidism or cancer in over 90% of cases. The rest of the etiologies are numerous. (2)Primary hyperparathyroidism is a pathologic and unregulated excess of PTH leading to elevated calcium. Malignancy is the most common cause of hypercalcemia that leads to inpatient care. Other less

frequent etiologies are bone diseases, granulomatous conditions, and diet. In the case of malignancy or granulomatous disease,

determining the etiology may be more important than the electrolyte imbalance itself.

Table 1. Calcium physiology

Hormone	Efect	Bone	Gut	Kidney
PTH	↑ Ca ↓ Po4	↑ Osteoclasts	Indirect / Vit. D	Ca reabsorbtion Po4 excretion
Vitamin D3	↑ Ca ↑ Po4	Indirect action	↑ Ca ↑ Po4 absorbtion	Indirect action
Calcitonin	↓ Ca ↓ Po4	Inhibate osteoclasts	Indirect action	Ca and Po4 excretion

Hyperparathyroidism:

Primary hyperparathyroidism ranges in severity from very mild and asymptomatic, to severe disease complicated by the consequences of bone loss, including fractures and osteitis fibrosa cystica (von Recklinghausen disease). Tertiary hyperparathyroidism occurs in chronic renal failure.

Malignancy:

Hypercalcemia may be associated with malignancies in two ways: bony involvement by the tumor may lead to massive osteoclastic activity (osteolytic lesions) when the calcium flux simply overwhelms homeostatic mechanisms; a variety of tumors release PTH-related peptide acting on PTH receptors [3]. From 25% to 30% of patients with cancer will develop hypercalcemia at some point over the course of their disease. Common malignancies that can lead to hypercalcemia include: multiple myeloma, leukemia, lung and breast cancer. When malignancies cause hypercalcemia, the tumor is typically very advanced. Malignancies which produce hypercalcemia may be associated with multiple endocrine neoplasia (MEN) type 1 and MEN type 2a or isolated familial hyperparathyroidism. There is an association of primary hyperparathyroidism with neurofibromatosis and von Hippel-Landau. In

rare instances a parathyroid carcinoma may account for the condition.

Less common etiologies:

Vitamin D is a fat-soluble vitamin that can become toxic when excessive amounts are taken in over time. Self-dosing or is the usual cause. Overdosing with 1,α-hydroxylated vitamin D metabolites (alfacalcidol or calcitriol) can easily result in hypercalcemia and chronic administration must be avoided or carefully monitored. Exaggerated supplementation with over-the-counter products can also readily and frequently lead to hypercalcemia. Vitamin D is also elevated in granulomatous disease such as sarcoidosis, berylliosis, tuberculosis. The mechanism is enhanced conversion of vitamin D by macrophages. **Endocrine diseases** such as hyperthyroidism can lead to hypercalcemia and almost always hypercalciuria as a consequence of rapid bone turnover; another pathologic conditions are adrenal insufficiency, pheochromocytoma, acromegaly. **Iatrogenic causes** includes milk-alkali syndrome caused by excess dietary milk or alkali (e.g., because of dyspepsia) or excess calcium supplementation (e.g., in postmenopausal women) [4]. Other drugs are lithium and vitamin A derivates, used for acne treatment and thiazides that affect renal mechanisms and rapid bone

turnover, thus both causing hypercalcemia that reverses when the drugs are stopped.

Immobilization in adolescents and young people (Paget disease) causes massive bone demineralization and hypercalcemia. Older patients can also be subject to this problem, but the robust state of bone mineralization in young people means there is a much larger mobile calcium pool to create and sustain the hypercalcemia. Excess bone metabolism of any etiology can lead to hypercalcemia.

Congenital causes: familial hypocalciuric hypercalcemia can be confused with hypercalcemia due to hyperparathyroidism as abnormal calcium sensing in the parathyroid glands and kidneys leads to mild elevation of PTH and reduced calcium excretion. Williams syndrome - is a rare neurodevelopmental disorder characterized by a distinctive, "elfin" facial appearance, along with a low nasal bridge, an unusually cheerful demeanor and ease with strangers; developmental delay coupled with strong language skills and cardiovascular problems, such as supraaortic stenosis and

transient hypercalcaemia.

Clinical presentation

First, the clinician should take a history detailing any bone pain to suggest malignancy in metastatic locations of the long bones. A history of weight loss would identify malignancy more likely than hyperparathyroidism. History may also identify symptoms of high calcium such as renal stones (typical of hyperparathyroidism, lethargy), easy fatigue, confusion, depression, irritability, constipation, and polyuria/polydipsia. Classic GI symptoms may also be present (nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis). Chronic symptoms are more consistent with hyperparathyroidism, whereas more recent onset of symptoms suggests malignancy. Symptoms from calcium elevation are typically not found unless the calcium is above 12 mg/deciliter. Severe symptoms and coma are likely to appear when calcium gets above 13 mg/deciliter [5, 6].

Table 2. Clinical signs of Hypercalcemia

Renal symptoms	Nervous system	Cardiac symptoms	GI system	Musculoskeletal system
Renal stones	CNS depression	QT shortening	Gastritis	Arthralgia
Polyuria	Decreased reflexes	Sinus tachycardia	Pancreatitis	Bone pain
Nycturia		Ventricular	Constipation	Spontaneous fractures
Hematuria		extrasystoles	Anorexia	

Laboratory data

The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy, together accounting for 90% of cases. They can be distinguished by ordering a serum PTH level and a simultaneous repeat calcium test. Total serum calcium is usually satisfactory but if there is an elevated or markedly depressed plasma protein concentration, the physiologically important fraction is ionized calcium. Normal serum or

plasma total calcium should be 8.5 to 10.5 mg/dl and the ionized calcium should be 4.6 to 5.1 mg/dl. The PTH is elevated in primary hyperparathyroidism, despite elevated calcium indicating a disconnect between the regulating hormone and the ion regulated. In malignancy, calcium is elevated either due to a humoral abnormality with a PTH-related peptide or due to bone destruction in metastases. In cases of malignancy, the PTH might even be very low or barely detectable since the elevated calcium should inhibit PTH

secretion.

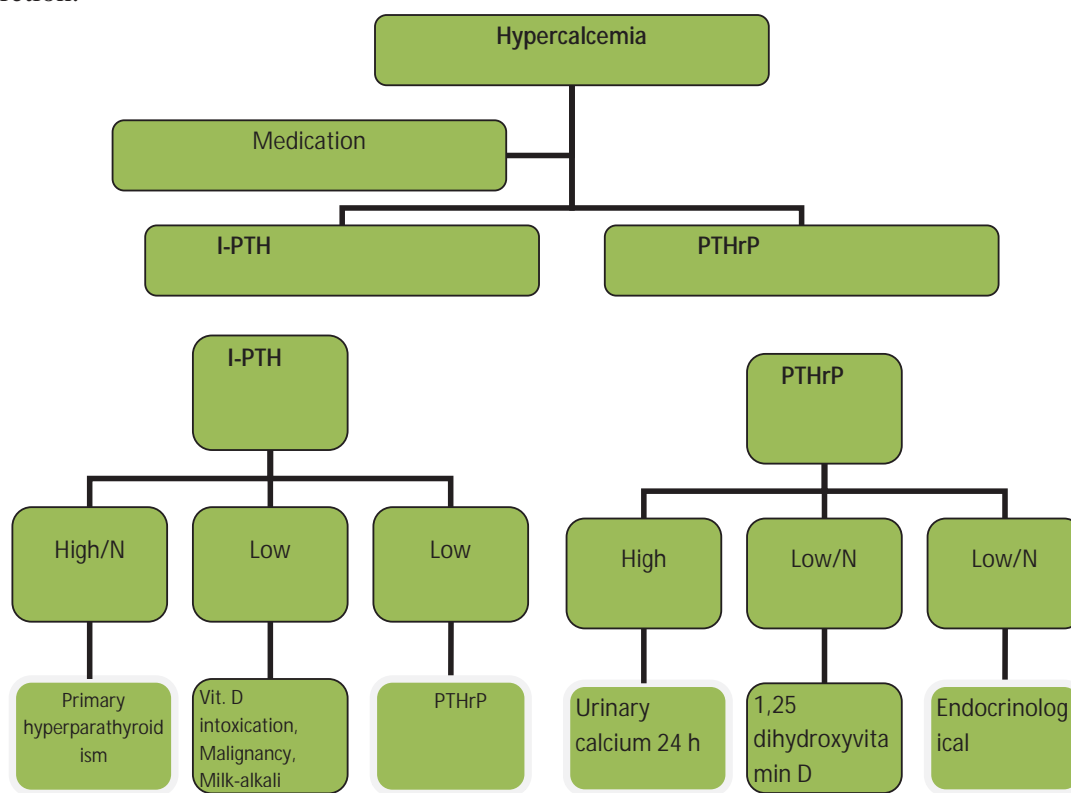


Figure 1. Laboratory work-up in hypercalcemia

Imaging Studies

Plain radiography may reveal demineralization, pathologic fractures, bone cysts, and bony metastases.

Renal imaging (ultrasonography, CT urography or intravenous pyelography) may find calcifications or stones.

Ultrasonography of the parathyroid glands is useful for hyperplasia or adenoma. A sestamibi nuclear scan may be helpful in locating a parathyroid adenoma [1].

Treatment

Treatment aims are the stabilization and reduction of serum calcium levels by adequate hydration with increased urinary excretion of calcium, by inhibition of osteoclasts in bone, by interruption of the drugs associated with hypercalcemia and by resolving the underlying cause.

The therapeutic options for hypercalcemia includes rehydration and diuretics,

biophosphonates, calcitonin. Initial treatment of hypercalcemia involves hydration to improve urinary calcium output. Isotonic sodium chloride solution is used, because increasing sodium excretion increases calcium excretion. Addition of a loop diuretic inhibits tubular reabsorption of calcium. Biophosphonates are studied mainly in adults but the usage of some of them is approved in children (etidronate and pamidronate). Calcitonin decrease skeletal reabsorption of calcium and inhibit renal reabsorption. Other therapeutic options include gallium nitrate, mithramycin, peritoneal dialysis or hemodialysis and new agents like calcimimetics (primarily indicated for chronic renal disease and secondary hyperparathyroidism) or calcitriol and other vitamin D analogues, such as paricalcitol. In [1,6,7] summary, every patient with serum calcium level superior to 12 mg % should underwent medical treatment, while values

above 14 mg% are considered an emergency (hypercalcemic crisis).

Surgical indications include serum calcium levels above 12 mg% at any age, severe "acute" hyperparathyroidism, hypercalciuria (more than 400 mg/day), renal lithiasis and impaired renal function, thinning of cortical bone in osteitis fibrosa cystica, low bone density, neuromuscular symptoms, age under 50 yrs (including children and teenagers). Surgical therapy aims to remove parathyroid in hyperparathyroidism, to resect PTH-secreting tumor and to treat orthopedic complications in bone metastases. Hypercalcemia can be associated in children with rare severe neonatal hyperparathyroidism but also with familial or sporadic nonMEN or MEN cases determined by adenomas, hyperplasias and even carcinomas. Surgical excision i.e adenomectomy, subtotal or total parathyroidectomy (with autotransplant) practiced early can provide quality and

prolonged healing.[7] No subtotal parathyroidectomy can be performed, or complete parathyroidectomy can be chosen with reimplantation of a small amount of tissue in the forearm in cases of renal hyperparathyroidism. In secondary hypercalcemia (majority of cases of malignant origin), together with the treatment of primary cause, administration of bisphosphonates, furosemide, corticoids, mithramycin, calcitonin may be useful. [8]

CONCLUSIONS

Hypercalcemia is often asymptomatic. The most common causes of hypercalcemia are primary hyperparathyroidism and malignancy. The etiology of hypercalcemia in children is age-dependent and includes a broad differential diagnosis. Although these conditions are not common, it is nevertheless important not to overlook them, as untreated hypercalcemia can have a profound impact on a child's growth and development.

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