Hypercalcemia in children and adolescents

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Purpose of review

In this review, we define hypercalcemia levels, common causes for hypercalcemia in children, and treatment in order to aid the practicing pediatrician.

Recent findings

One rare cause of hypercalcemia in the child is familial hypocalciuric hypercalcemia (also termed familial benign hypercalcemia). Mutations that inactivate the Ca^{2+}-sensing receptor gene *FHH* have been described as an autosomal dominant disorder, but recently milder mutations in the *CASR* have been shown to cause hypercalcemia when homozygous.

Summary

Normal serum levels of calcium are maintained through the interplay of parathyroid, renal, and skeletal factors. In this review, we have distinguished the neonate and infant from the older child and adolescent because the causes and clinical features of hypercalcemia can differ in these two age groups. However, the initial approach to the medical treatment of severe or symptomatic hypercalcemia is to increase the urinary excretion of calcium in both groups. In most cases, hypercalcemia is due to osteoclastic bone resorption, and agents that inhibit or destroy osteoclasts are, therefore, effective treatments. Parathyroid surgery, the conventional treatment for adults with symptomatic primary hyperparathyroidism, is recommended for all children with primary hyperparathyroidism.

Keywords

bisphosphonates, hypercalcemia, hyperparathyroidism, pediatrics

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Introduction

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. Normal serum levels of calcium are maintained through the interplay of parathyroid, renal, and skeletal factors. The principal calciotropic hormone is parathyroid hormone (PTH), which is synthesized and secreted from the parathyroid glands at a rate inversely proportional to the circulating level of ionized calcium. PTH secretion is regulated through the interaction of extracellular calcium with specific calcium-sensing receptors (CaSRs) that are present on the surface of the parathyroid cell. In turn, PTH regulates mineral metabolism and skeletal homeostasis by activating specific membrane receptors on target cells in bone and kidney that bind PTH and the related hormone PTH-related peptide (PTHrP) with equal affinity. In the kidney, PTH stimulates conversion of 25(OH)D to calcitriol [$1,25(OH)_2D$], the active metabolite of vitamin D. Both PTH and calcitriol activate osteoclastic bone resorption and increase renal absorption of filtered calcium, whereas calcitriol can also increase active transport of calcium in the intestine. Although absorption of too much calcium from the intestine can account for some cases of hypercalcemia, in most patients hypercalcemia is due to excessive osteoclastic activity. PTH and other factors that stimulate osteoclastic activity interact directly with receptors on osteoblasts, the bone forming cells, to increase their expression of RANKL [TRANCE (tumor necrosis factor-related activation-induced cytokine) is another term for RANKL], a ligand that binds to the receptor activator of neutral factor-kappa B (RANK) on osteoclast precursors, and to decrease production of osteoprotogerin, a circulating decoy receptor for RANKL. RANKL stimulates activation, migration, differentiation, and fusion of hematopoietic cells of the osteoclast lineage to stimulate bone resorption [1,2].

Serum calcium concentrations are higher in children than in adults (Table 1 [3]); therefore, the diagnosis of hypercalcemia in younger patients requires use of age-appropriate normal ranges. In this review, we have distinguished the neonate and infant from the older child and adolescent because the causes and clinical features of hypercalcemia can differ in these two age groups.

Table 1 Representative normal values for age for concentrations of serum total calcium

	Age (years)	Serum total calcium (mg/dl)
Infants	0–0.25	8.8–11.3
	1–5	9.4–10.8
Children	6–12	9.4–10.3
Men	20	9.1–10.2
	50	8.9–10.0
	70	8.8–9.9
Women	20	8.8–10.0
	50	8.8–10.0
	70	8.8–10.0

Data from [3].

Diagnosis of hypercalcemia in neonates and infants

The differential diagnosis of hypercalcemia in neonates and infants up to the age of 2 years is listed in Table 2 [4,5]. Clinical features of hypercalcemia may be nonspecific in neonates and infants, and hypercalcemia is often discovered when a chemistry panel is obtained to evaluate failure-to-thrive. Severe hypercalcemia can affect the nervous system and cause weakness, hypotonia with proximal myopathy, lethargy and stupor, and rarely seizures. Hypercalcemia can also induce polyuria and dehydration, as stimulation of the renal CaSRs in the collecting tubule decreases expression of aquaporin-2 at the apical plasma membrane [6,7] and leads to resistance to vasopressin and diabetes insipidus. In addition, there can be damage to the kidneys from nephrocalcinosis [4,5].

In the small infant, enriched formulas that provide excess calcium can quickly lead to hypercalcemia. Phosphate depletion can cause a defect in mineralization and hypercalcemia, and in the past often resulted from human milk feeding in preterm, very-low-birth-weight infants [4,5]. The introduction of breast milk fortifiers, which contain 30–40 mg/kg per day of phosphate, for these infants has all but eliminated phosphate depletion. By contrast, a far more common cause of phosphate depletion is from inappropriately supplemented parenteral nutrition [8,9]. Hypophosphatemia suppresses circulating levels of fibroblast growth factor 23, a phosphate-regulating hormone or 'phosphatonin', with subsequent disinhibition of calcitriol production. Elevated serum levels of calcitriol stimulate intestinal absorption of calcium and activate osteoclastic bone resorption. Finally, extracorporeal membrane oxygenation can also cause hypercalcemia, but the mechanism is unclear [10].

Table 2 Differential diagnosis of hypercalcemia in neonates and infants (up to 2 years of age)

Iatrogenic
Phosphate depletion
Premature infants on human milk or standard formula
Parenteral nutrition
Hyperparathyroidism
Congenital parathyroid hyperplasia
Maternal hypoparathyroidism
Inactivating mutations in Ca^{2+}-sensing receptor gene
Familial hypocalciuric hypercalcemia (familial benign hypercalcemia)
Neonatal severe hyperparathyroidism
Jansen's metaphyseal chondrodysplasia
Persistent PTHrP
Hypervitaminosis D
Subcutaneous fat necrosis
Williams syndrome/idiopathic infantile hypercalcemia
Other inborn metabolic disorders
Blue diaper syndrome
Lactase deficiency
Disaccharide intolerance
Bartter syndrome
Hypophosphatasia
IMAGe
Down syndrome
Severe congenital hypothyroidism
Maternal hypercalcemia
Vitamin A intoxication

PTHrP, parathyroid hormone-related peptide.

Neonatal hyperparathyroidism

Neonatal hyperparathyroidism is uncommon, and is usually due to multi-gland hyperplasia rather than to parathyroid adenoma as in older patients [11]. Severe bone deformities, as well as fractures, may be present at birth and reflect impaired mineralization and intense osteoclastic bone resorption. Respiratory difficulties can occur if the rib cage is affected. There may be hepatosplenomegaly and anemia. Failure to normalize the serum calcium level can have profound developmental implications [12].

In some infants, neonatal hyperparathyroidism represents an adaptation to maternal hypocalcemia, most commonly not only from maternal hypoparathyroidism or vitamin D deficiency [13] but also from pseudohypoparathyroidism [14] and renal tubular acidosis [15]. Serum calcium levels are generally normal but hypercalcemia has been reported in 25% of these infants [16]. Hyperparathyroidism typically resolves within a few weeks.

Familial hypocalciuric hypercalcemia (FHH) (also termed familial benign hypercalcemia) is characterized by asymptomatic hypercalcemia and very low levels of urinary calcium. Mutations that inactivate the Ca^{2+}-sensing receptor gene (*CASR*), localized to chromosome 3q, are the most common cause of FHH, and are also associated with neonatal severe hyperparathyroidism (NSHPT), a life-threatening form of primary hyperparathyroidism that is associated with very high levels of serum calcium and PTH. FHH and NSHPT can occur in the same family, and represent the presence of one or two defective *CASR* alleles, respectively [17–21]. NSHPT can also occur in heterozygous offspring born to affected fathers but unaffected normocalcemic mothers, or in neonates with an apparent de-novo heterozygous mutation in the *CASR* gene [22,23•]. In addition to hypercalcemia, infants with NSHPT have hypophosphatemia and osteopenia at birth [20]. The bone disease is likely a reflection of

both elevated PTH and decreased *CASR* activity in osteoblasts and osteoclasts [24].

Reduced expression of CaSRs decreases the sensitivity of the parathyroid cells to extracellular Ca^{2+} and leads to mild hyperplasia of all parathyroid glands. The CaSR is also expressed in the kidney, and decreased receptor activity in the distal nephron accounts for the relative hypocalciuria (i.e., the fractional excretion of calcium is less than 1%) that is the hallmark of the disorder.

Conventional treatment of NSHPT has been urgent subtotal parathyroidectomy, but intravenous bisphosphonates may be used to reduce the serum calcium level quickly and either delay or obviate surgery [23•,25]. Recent studies of calcimimetic compounds, which activate the parathyroid cell CaSR and inhibit PTH secretion, in adult patients [26] and a single adolescent [27] with primary hyperparathyroidism suggest that these agents may be useful medical alternatives or adjuncts to surgery for control of hypercalcemia. Type I calcimimetics are direct receptor agonists, whereas type II calcimimetics are allosteric activators that interact with the membrane-spanning segments of the CaSR and enhance signal transduction, presumably by inducing conformational changes in the receptor. The presumed conformational change reduces the threshold for CaSR activation by the endogenous ligand, Ca^{2+}, thereby reducing PTH secretion in the absence of a change in the level of extracellular Ca^{2+}. Type II calcimimetics have been shown *in vitro* to enhance the potency of extracellular Ca^{2+} to activate mutant CaSRs [28,29] and have been used successfully in an older patient with FHH and symptomatic hypercalcemia [30], but efficacy in children with FHH or NSPHT has not been reported.

FHH is typically an autosomal dominant disorder, but some milder mutations in the *CASR* only cause hypercalcemia when homozygous [31•]. In nearly all cases, FHH (and NSHPT) is due to mutation of the *CASR* gene, but the disorder has been also linked to the long [32,33] and short [34] arms of chromosome 19, indicating genetic heterogeneity for this disorder.

Nonparathyroid causes of hypercalcemia

Hypercalcemia may be a manifestation of vitamin D intoxication in newborns whose mothers ingested excessive amounts of vitamin D, its derivatives, or both during pregnancy [14]. Because of the tight regulation of renal 25(OH)D-1-α-hydroxylase in the kidney, serum levels of 25(OH)D but not calcitriol are elevated in these infants. By contrast, serum levels of calcitriol are markedly elevated in hypercalcemic infants with subcutaneous fat necrosis, an unusual disorder that occurs in some neonates after a complicated delivery. Hypercalcemia can occur days or weeks after birth, and results from production of excess calcitriol by macrophages within the granulomatous reaction to the necrotic fat. Calcium released from necrotic fat tissue and increased prostaglandin E activity further aggravate hypercalcemia [35–37]. Failure-to-thrive is the most common clinical sign associated with subcutaneous fat necrosis, which is associated with a significant 15% mortality [37].

Williams syndrome is associated with hypercalcemia in approximately 15% of cases. Hypercalcemia typically occurs during infancy and resolves between 2 and 4 years of age. There are cases, however, of older children and adults who have persistent hypercalcemia. Circulating levels of calcitriol are elevated in some but not all patients with Williams syndrome, and PTH levels are low [38]. A common finding is increased sensitivity to vitamin D, which appears to be due to decreased ability of ligand-bound vitamin D receptor (VDR) to mediate transrepression of the $25(OH)D_3$-1α-hydroxylase gene, *CYP27B1*. A potential explanation for this defect is haploinsufficiency of the Williams syndrome transcription factor (WSTF), which is located within the 7q11.23 deleted region. The VDR interacts with a multifunctional, ATP-dependent chromatin remodeling complex termed WINAC in a ligand-independent manner through WSTF, and loss of WSTF prevents calcitriol-bound VDR-induced transrepression of *CYP27B1* [39,40].

Inborn errors of metabolism that cause hypercalcemia

Hypophosphatasia, a metabolic bone disease characterized by bone and teeth hypomineralization due to defective function of tissue-nonspecific alkaline phosphatase, is also associated with hypercalcemia. Hypophosphatasia is caused by various mutations in the *ALPL* gene at 1p34–36 [41–44], and is classified into six clinical forms depending on the age at diagnosis and the severity of the symptoms: perinatal lethal, infantile, childhood, adult, odontohypophosphatasia, and perinatal benign. Infantile hypophosphatasia presents before the age of 6 months and can cause severe hypercalcemia. Deficiency of alkaline phosphatase impairs skeletal mineralization and calcium uptake, leading to hypercalcemia with hypercalciuria and nephrocalcinosis. Affected infants have respiratory complications due to rachitic deformities of the chest. Despite the presence of an open fontanelle, premature craniosynostosis is a common finding that may result in increased intracranial pressure. Serum levels of total and bone-specific alkaline phosphatase are low, and the diagnosis is supported by the presence of very high levels of urinary phosphoethanolamine. Mutational analysis of the *ALPL* gene can provide molecular confirmation. In infants who survive, there is often spontaneous improvement in mineralization and remission of clinical problems, with the exception of craniosynostosis. Although there is no known treatment

of hypophosphatasia, some patients have shown improvement after transplantation of bone marrow, bone, or mesenchymal stem cells [45]. A bone-targeted form of enzyme replacement therapy [46] is now undergoing clinical trials.

Blue diaper syndrome is an uncommon metabolic disorder that is due to a defect in tryptophan metabolism [47]. The block in tryptophan metabolism leads to urinary excretion of excessive amounts of indole derivatives, including a derivative called 'indican' that gives the urine-soaked diaper a blue tint. Affected infants have hypercalcemia, hypercalciuria, and nephrocalcinosis, but the mechanism is unknown.

Hypercalcemia has been described in infants with congenital lactase deficiency. Hypercalcemia typically resolves after initiation of a lactose-free diet, but hypercalciuria and nephrocalcinosis may persist [48]. The cause of the hypercalcemia is unclear, but may be due to metabolic acidosis, an increase in intestinal calcium absorption secondary to increased gut lactose, or both [48]. A similar mechanism may explain hypercalcemia in infants with disaccharide intolerance [49].

Bartter syndrome is commonly associated with hypercalciuria [50], but hypercalcemia has been described in some infants with homozygous inactivation in the gene for either the furosemide-sensitive NaK-2Cl-cotransporter NKCC2 (*SLC12A1*) or the inwardly rectifying potassium channel ROMK (*KCNJ1*) [51,52].

Hypercalcemia, hypercalciuria, or both can also occur in children with the IMAGe syndrome, a poorly defined disorder that consists of intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital defects [53]. Neither the molecular defect nor the basis for hypercalcemia has been identified.

Hypercalcemia in older children

A list of biochemical features that aid in the differential diagnosis of hypercalcemia in children is presented in Table 3, and an algorithm for evaluation of the child with hypercalcemia is presented in Fig. 1 [54]. In older children, primary hyperparathyroidism, immobilization, and malignancy are the principal causes of hypercalcemia.

Primary hyperparathyroidism in children and adolescents

Primary hyperparathyroidism is usually sporadic in the child or adolescent, and is nearly always (65%) due to a single parathyroid adenoma. The age range is from 3 to 19 years with a mean of 12.8 years and a 3 : 2 female : male incidence [55]. Primary hyperparathyroidism is far less common in children and adolescents than in adults. Nearly all patients (79%) are symptomatic at presentation and end-organ damage (nephrocalcinosis, nephrolithiasis, acute pancreatitis, or bone involvement) is common (44%).

Primary hyperparathyroidism can also be an autosomal dominant genetic disorder that is typically associated with multi-gland hyperplasia [56]. Primary hyperparathyroidism is most commonly (57%) the presenting manifestation of multiple endocrine neoplasia (MEN) type I [55], but can also be the initial feature of the hyperparathyroidism–jaw tumor syndrome, which is associated with parathyroid carcinoma [57,58]. Primary hyperparathyroidism is less often a manifestation of MEN type II. Children with asymptomatic, mild hypercalcemia are likely to have FHH.

Nonparathyroid causes of hypercalcemia in older children and adolescents

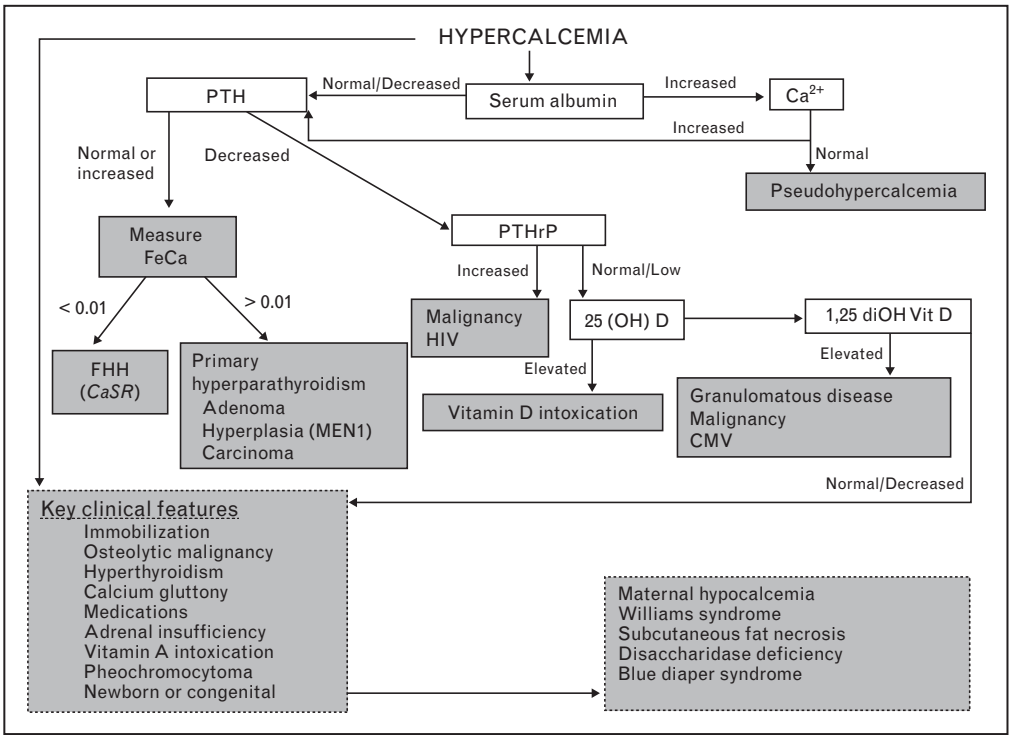
Hypervitaminosis D can occur in children who ingest excessive amounts of vitamin D (or its metabolites). Although the upper limit of vitamin D tolerability for adults is 10 000 units per day, over time young children and infants may develop vitamin D intoxication when receiving only 2000–4000 units daily [14,54]. Serum levels of 25(OH)D are elevated, but serum levels of calcitriol are usually normal; PTH levels are suppressed. Endogenous vitamin D intoxication can occur in patients with granulomatous disease and other inflammatory disorders. Infectious diseases such as cat scratch fever [59] as well as histoplasmosis, coccidiomycosis, leprosy, and

Table 3 Laboratory values in differential diagnosis of hypercalcemia

	Serum calcium	Serum phosphorus	Fractional excretion of calcium	PTH	PTHrP	25(OH)D	1,25(OH)2D
Familial hypocalciuric hypercalcemia	↑	N or ↓	< 0.01	N or ↑	↓	N	↑
NSHPT	↑↑↑	↓	<0.01	↑↑	↓	N or ↓	↑
Subcutaneous fat necrosis	↑	↑	↑	↓	↓	N	↑↑
Williams syndrome	↑	↑	↑	↓	↓	N	N or ↑
Primary hyperparathyroidism	↑	↓	>0.01	↑	↓	N	↑
Humoral malignancy	↑↑	↓	↑	↓	↑↑	N	N or ↑
Osteolytic malignancy	↑↑	↑	↑↑	↓	↓	N	↓
Granulomatous disease	↑	↑	↑↑	↓	↓	N	↑↑
Vitamin D intoxication	↑	↑	↑↑	↓	↓	↑↑	N or ↓
Immobilization	↑	↑	↑↑	↓	↓	N	↓

N, normal; NSHPT, neonatal severe hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide.

Figure 1 Hypercalcemia algorithm



CaSR, calcium-sensing receptor; CMV, cytomegalovirus; FeCa, fractional (urinary) excretion of calcium; FHH, familial hypocalciuric hypercalcemia; MEN1, multiple endocrine neoplasia type 1; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related hormone. Adapted with permission from [54].

tuberculosis have all been associated with hypercalcemia in children. In these conditions, activated T cells and macrophages express 25-(OH)D-1-α hydroxylase activity, which converts 25(OH)D to calcitriol [60].

Immobilization

Immobilization is a common cause of hypercalciuria in children and adolescents and can also cause hypercalcemia. When a rapidly growing child is immobilized or placed on bed rest, there is a marked decrease in osteoblastic bone formation and a corresponding increase in osteoclastic bone resorption. This imbalance in bone remodeling leads to excessive mobilization of calcium (and phosphate) from the skeleton; the consequent net loss of bone mass is designated disuse osteoporosis [61].

Hypercalcemia of malignancy

Hypercalcemia occurs in fewer than 1% of children with cancer, and has been reported with leukemia, lymphoma, myeloma, neuroblastoma, hepatocellular carcinoma, ovarian carcinoma, hepatoblastoma, rhabdomyosarcoma, brain cancer, and dysgerminomas. Malignancy-associated hypercalcemia can be attributed to two general mechanisms: osteolytic, due to direct invasion of the skeleton by tumor cells, and humoral, due to tumor production of circulating factors that activate osteoclastic bone resorption. The most commonly identified humoral factor that causes hypercalcemia of malignancy is PTHrP. PTHrP normally acts as a paracrine and intracrine factor, but some tumors can secrete sufficient PTHrP into the circulation to induce hypercalcemia via interaction with the type 1 PTH/PTHrP receptor. The specific tumors that characteristically produce humoral hypercalcemia of malignancy via secretion of PTHrP include squamous cell carcinoma of the lung, head, and neck; renal cell carcinoma; breast and ovarian carcinoma; adult T-cell leukemia; and dysgerminoma. Other tumor-produced factors that play a role in producing hypercalcemia include calcitriol, prostaglandins, interleukin (IL)-1 and IL-6, transforming growth factor-beta, and tumor necrosis factor.

Miscellaneous causes

A variety of unusual causes of hypercalcemia must be considered in children who do not have any of the disorders discussed above (Table 4). Hypercalcemia can occur after chronic ingestion of vitamin A. The child develops anorexia, pruritus, irritability, bone pain, and tender swellings of bone. Associated features include osteopenia due to increased osteoclastic bone resorption, hyperostosis of the shafts of the long bones, and osteophyte formation, particularly in the thoracic spine. Severe hypercalcemia has also been associated with the administration of the

Table 4 Hypercalcemia in children (over 2 years of age) and adolescents

Excessive calcium intake
Phosphate depletion
Parenteral nutrition
Hyperparathyroidism
Acquired primary
adenoma
multiglandular
carcinoma
Genetic primary
autosomal dominant/recessive FHH
familial
MEN types I and IIa (IIb)
Hyperparathyroidism–Jaw tumor
Autonomous (tertiary)
Hypervitaminosis D
Excessive intake
Granulomatous diseases: cat scratch fever; sarcoidosis; tuberculosis; histoplasmosis; coccidiomycosis; leprosy; HIV
Chronic inflammatory disorders
Williams syndrome/idiopathic infantile hypercalcemia
Immobilization
Malignancy associated hypercalcemia
Primary bone tumors
Metastatic tumors with osteolysis
Tumors secreting PTHrP, prostaglandins, cytokines, and growth factors
Hepatic disease
Hyperthyroidism
Adrenal insufficiency
Pheochromocytoma
Vasoactive intestinal polypeptide-secreting tumor
Drugs (thiazides, lithium, systemic retinoid derivatives, theophylline, and acetosalicylic acid)
Milk alkali syndrome/calcium gluttony
Renal tubular acidosis

FHH, familial hypocalciuric hypercalcemia; MEN, multiple endocrine neoplasia; PTHrP, parathyroid hormone-related peptide.

vitamin A analogue all-*trans*-retinoic acid during therapy for acute promyelocytic leukemia.

Children with Jansen metaphyseal chondrodysplasia have hypercalcemia and bone lesions that are typical of primary hyperparathyroidism, but have suppressed PTH levels. This unusual disorder is due to mutations in the *PTHR1* gene encoding the type 1 PTH/PTHrP receptor that leads to ligand-independent activation of signaling. This causes increased bone resorption, metaphyseal defects, elevated serum levels of calcitriol, and growth delay.

Treatment

The initial approach to the medical treatment of severe or symptomatic hypercalcemia is to increase the urinary excretion of calcium. Infants are frequently dehydrated, and 0.9% saline containing 30 mEq of potassium chloride per liter should be infused to correct dehydration and maximize glomerular filtration rate. Furosemide and other powerful loop diuretics are rarely necessary, and can induce excessive diuresis and dehydration; the consequent fall in the glomerular filtration rate can worsen hypercalcemia.

In most cases, hypercalcemia is due to osteoclastic bone resorption, and agents that inhibit or destroy osteoclasts will be effective treatments. Calcitonin (2–4 U/kg per 12 h) given by subcutaneous injection is effective at first, but resistance to the hormone occurs quite rapidly. The nitrogen-containing bisphosphonates, including alendronate, ibandronate, pamidronate disodium, risedronate, and zoledronic acid, induce osteoclast apoptosis and are potent inhibitors of bone resorption. Zoledronic acid is a new-generation, heterocyclic nitrogen-containing bisphosphonate and the most potent inhibitor of bone resorption identified to date. Both pamidronate disodium and zoledronic acid can rapidly lower serum and urinary calcium levels in patients with hypercalcemia due to a variety of causes, and the effects can last for weeks. Patients must be monitored carefully, as these powerful agents can cause severe hypocalcemia, hypophosphatemia, and hypomagnesemia. In addition, approximately 20% of patients will experience an untoward acute phase reaction after receiving an initial intravenous infusion. There is increasing concern about the development of osteonecrosis of the jaw in patients who are receiving chronic or prolonged bisphosphonate therapy. Adult patients with multiple myeloma and metastatic carcinoma to the skeleton who receive multiple, frequent doses of intravenous, nitrogen-containing bisphosphonates appear to be at greatest risk for osteonecrosis of the jaw, and these patients account for nearly all published cases. The mandible is more commonly affected than the maxilla (2 : 1 ratio), and most cases are preceded by a recent dental surgical procedure [62]. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. Osteonecrosis of the jaw has not been reported in children who are receiving bisphosphonates.

Because of the low frequency of hypercalcemia in children, comprehensive clinical trials on the safety and efficacy of the bisphosphonates in children are lacking, although several small studies [25,63–65] have reported promising results for these agents in the treatment of young patients with hypercalcemia. In particular, bisphosphonates can rapidly reverse the hypercalcemia and hypercalciuria of immobilization [66].

Because of concerns regarding potential late adverse effects of bisphosphonates on growth and development of the skeleton, calcitonin tends to be used more frequently in children because it has no long-term sequelae. Glucocorticoid steroids, which are effective treatments for hypercalcemia associated with vitamin D excess, are used with caution in children because they impair linear growth and bone mineralization. Children with Williams syndrome or idiopathic infantile hypercalcemia often have mildly elevated serum levels of calcitriol, and a low calcium formula in the infant or reduced calcium diet

in the older child may be all that is needed to treat the hypercalcemia, hypercalciuria, or both, particularly when long-term treatment will be necessary. CalciloXD (Ross Laboratories, North Chicago, Illinois, USA) is a low-calcium infant formula without vitamin D that is commonly used. As the hypercalcemia improves, the CalciloXD can be gradually mixed with regular formula or breast milk. The infants and children on the low-calcium diet need to be followed closely, however, for the possible development of hypocalcemia and rickets.

Parathyroid surgery, the conventional treatment for adults with symptomatic primary hyperparathyroidism, is recommended for all children with primary hyperparathyroidism. Indeed, the younger age of pediatric patients provides an even more compelling justification for recommending surgery for most patients. Of course, hypercalcemic children with FHH will rarely require any intervention unless they have NSPHT, and then parathyroidectomy may be necessary. The calcimimetic cinacalcet has been used in small studies of children and adolescents with hyperparathyroidism secondary to renal failure, and effectively lowers serum calcium and PTH, but does not alter bone turnover or increase bone mineral density [67•].

Conclusion

The cause of hypercalcemia in children is age-dependent and includes a broad differential diagnosis (Table 3 and Fig. 1). 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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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 555).

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