

Parathyroid Disorders

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Practice Gap

Hypocalcemia is not uncommon in pediatric practice, but hypercalcemia is. Clinicians should improve their ability to recognize the variants in the differential diagnosis related to parathyroid diseases.

Objectives After completing this article, readers should be able to:

1. Describe the differential diagnosis of parathyroid diseases that result in hyper- and hypocalcemia.
2. Delineate the approach to making the diagnosis of parathyroid diseases and necessary therapies.

INTRODUCTION

Parathyroid hormone (PTH) is a peptide hormone that is the primary regulator of calcium concentrations in the bloodstream. PTH is released in response to a variety of signals, most importantly in response to low serum calcium concentrations. As a true hormone, it travels through the bloodstream to target tissues, primarily in the bone and kidney, where it has a variety of effects that serve to increase serum calcium, thus providing a correction for the original stimulus for release. PTH serves as an important regulator of bone turnover and in different settings can have either anabolic or catabolic effects in bone. Although PTH can mobilize phosphorus and calcium in bone, it also increases phosphate excretion, resulting in a net lowering of phosphate concentrations in the bloodstream. Given its central role in this important homeostatic process, a number of disorders are caused by abnormalities of PTH function.

BIOCHEMISTRY

PTH is an 84-amino acid protein, with the first 34 amino acids being essential for full activity. (1) PTH signals through a G-protein-coupled receptor. (1) PTH shares this receptor with another peptide, PTH-related peptide (PTHrP), which is a paracrine factor that has important functions throughout the body, including regulation of the growth plates. That 2 peptides share the same receptor becomes important when considering the phenotypes of pathologic conditions involving either overproduction of PTH or PTHrP or activating and inactivating mutations of the PTH/PTHrP receptor. The PTH/PTHrP receptor signals primarily through the G-protein G_{α} , triggering intracellular signaling via activation of adenylate cyclase and increasing intracellular concentrations of

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cyclic adenosine monophosphate (cAMP). The PTH/PTHrP receptor can also signal through an inositol triphosphate mechanism and through direct interactions with the intracellular scaffold protein NHERF-1 and NHERF-2. (2)

REGULATION

PTH is produced in the 4 parathyroid glands, which are found near the thyroid gland. PTH can also be produced within the thymus in some individuals. PTH release is primarily regulated by serum calcium. Decreased serum calcium leads to decreased binding of calcium to the calcium-sensing receptor (CaSR). (3) This, in turn, activates phospholipase C, which increases uptake of calcium into intracellular stores. The decreased intracellular calcium concentrations cause fusion of PTH-containing vesicles with the cell membrane, (4) releasing PTH into the circulation. Several other stimuli can increase PTH release, including increased serum phosphorus and decreased 1,25-dihydroxyvitamin D (1,25D) concentrations.

BIOLOGICAL EFFECTS

The key target tissues for PTH are bone, kidney, and skin. In the bone, PTH/PTHrP receptors can be found on osteoblasts, and PTH has the direct effect of stimulating osteoblasts to induce bone formation. (5) However, once stimulated, osteoblasts express receptor activator of nuclear factor κ -B ligand (RANKL) and macrophage colony-stimulating factor, which can induce differentiation of preosteoclasts into osteoclasts. Osteoblasts also produce osteoprotegerin, which is an inhibitor of RANKL. Depending on dose and duration of exposure to PTH, these can lead to either net anabolic or catabolic effects in bone (6)(7) but always result in increased bone turnover.

In the kidneys, PTH acts in the proximal convoluted tubule to increase concentrations of 1- α -hydroxylase, the enzyme that converts 25-hydroxyvitamin D into its active form, 1,25D. 1,25D exerts its primary effect in the intestine to increase absorption of calcium and, to a lesser extent, phosphorus (Fig 1). PTH also acts directly in the distal convoluted tubule and thick ascending limb of the nephrons to increase calcium reabsorption, but with sustained increases in PTH, the increased serum calcium from PTH's other actions overrides this effect, resulting in net increased calcium excretion. The actions of PTH in the kidney are most critical to its ability to increase serum calcium, as is evident in the disorder pseudohypoparathyroidism (PHP), where a selective renal resistance to PTH results in severe hypocalcemia. (8)

Although PTH has a net effect in the body of increasing serum calcium, it has opposite effects on serum phosphorus. Activation of bone formation and ultimately bone removal release phosphorous stores from bones, but potent effects in the kidney to increase phosphorus excretion cause a net decrease in serum phosphorus. These effects are mediated through downregulation of the sodium phosphorus co-transporters NaPi-2A and NaPi-2C in the proximal convoluted tubule. (9) The net loss occurs despite direct effects of 1,25D to increase intestinal phosphorus absorption and decrease phosphorus excretion in the kidney.

HYPOPARATHYROIDISM

Normally, the parathyroid glands respond to a decrease in extracellular calcium concentration, detected by the membrane-bound CaSR, by releasing preformed PTH into blood and initiating the cellular production of more hormone. Failure of the glands to respond normally to this signal is termed hypoparathyroidism. It is characterized by inappropriately low PTH concentrations relative to the degree of hypocalcemia. When PTH is produced and released into the circulation appropriately but fails to have calcemic effects, it is termed pseudohypoparathyroidism (PHP). Regardless of cause, the common finding is low extracellular calcium concentrations. The hallmark symptoms are related to the associated hypocalcemia.

Hypoparathyroid Disease

Clinical Presentation. Hypocalcemia-related events lead to the suspicion of parathyroid diseases. The classic findings are neuromuscular, resulting in sustained or intermittent involuntary contractions termed tetany. These may occur in the hands and feet, presenting typically with the fingers extended and ulnar deviated, with thumb folded in underneath the fingers (Fig 2).

Although rigid, the fingers can be bent. Upon release, they spring back to the extended position and remain so until hypocalcemia is corrected. Intermittent contractions of large muscle groups are recognized as seizures. Typically they are short, lasting 1 minute or less, but repetitive. An initial lack of a postictal phase after the first events can lead to confusion as to whether a seizure has actually occurred. With recurrences, fatigue sets in and patients can appear lethargic. Contraction in the airway, especially in the larynx, causes stridor with partial occlusion and cyanosis with complete occlusion. Bronchospasm can present as wheezing. Other nonhypocalcemia-induced symptoms that may be present and are related to the cause are discussed in the review of the differential diagnoses.

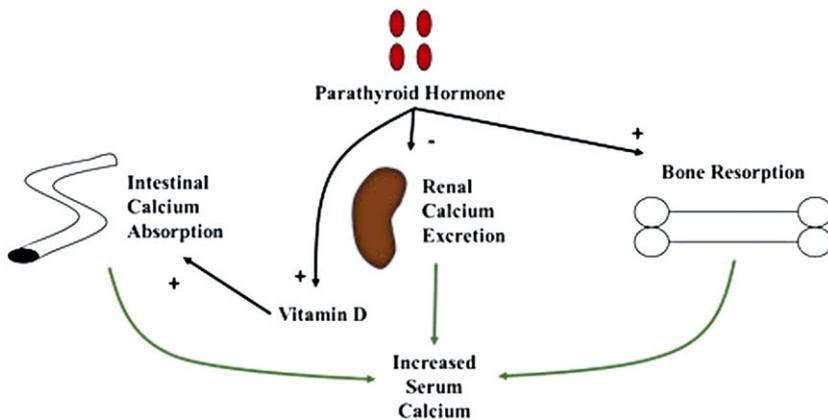


Figure 1. Parathyroid hormone regulation of serum calcium.

Clinical Signs. The easy irritability of the neuromuscular system allows for bedside signs. The Chvostek sign is elicited by tapping on the facial nerve as it surfaces to the cheek right under the maxillary bone about 1 to 2 cm anterior to the tragus of the ear. A positive sign occurs when the tap results in a twitch at the corner of the mouth on the ipsilateral side. The Trousseau sign is performed by inflating an arm cuff above systolic blood pressure and keeping it inflated for 3 to 5 minutes. A positive sign consists of a complaint of tingling in the hand and the development of tetany. A QTc interval of greater than 0.425 on electrocardiography is consistent with hypocalcemia.

Radiographic and Laboratory Findings. Radiographic findings include: shortened fourth and fifth metacarpals and metatarsals (see the section on pseudohypoparathyroidism type Ia) and calcifications of the basal ganglia in longstanding cases (generally >8 years). (10) The latter may contribute to central nervous system (cognitive) dysfunction. (11) In addition to hypocalcemia, hyperphosphatemia with alkaline phosphatase in the normal range is found on laboratory analyses.

Differential Diagnosis. There are both congenital and acquired causes of hypoparathyroidism, which are summarized in Fig 3.

An explosion in gene identification has contributed to the understanding of hypoparathyroidism. Mutations that cause embryologic deficiencies can result in absent or underdeveloped (hypoplastic) parathyroid glands. Examples of single-gene causes include the embryologic development factors: *Hoxa3*, *Pax1*, *Eya1*, *Six1*, and *GCM2*. Deletion of the gene coding for the transcription factor *GATA3* results in the triad of hypoparathyroidism, deafness, and renal dysplasia (Barakat syndrome). (12) Mutations in the gene encoding tubulin-specific chaperone E (*TBCE*) results in either the Sanjad-Sakati syndrome in which hypoparathyroidism is accompanied by failure to thrive, microcephaly, and marked

intellectual disability, or Kenny-Caffey syndrome, in which intelligence can be normal but skeletal findings are marked by thickened long bones at birth. (13)

The responsiveness to extracellular calcium is dependent on the CaSR located on the surface of the parathyroid cell. Low calcium concentrations in blood result in intracellular signal transduction via this G-protein-coupled receptor, leading to the production and release of PTH. Gain-of-function mutations in the CaSR gene result in diminished parathyroid responsiveness to low calcium concentrations. (14) Finally, the parathyroid glands may be present, the CaSR responsive, and the intracellular machinery for PTH functional, but the gene coding for PTH is mutated, resulting in a nonfunctional or absent circulating product.

Chromosomal microdeletions (22q11.2, 10p15.3p14) also can result in hypoplastic or absent parathyroid glands in association with defined syndromes. The best known of these is DiGeorge syndrome (velocardiofacial syndrome), which includes maldevelopment of tissues between the



Figure 2. Tetany of the hand. Reprinted with the permission of Medchrome, courtesy of Sujit Kumar Shrestha, MD, Pediatrics (TUTH), Nepal Medical College Teaching Hospital.

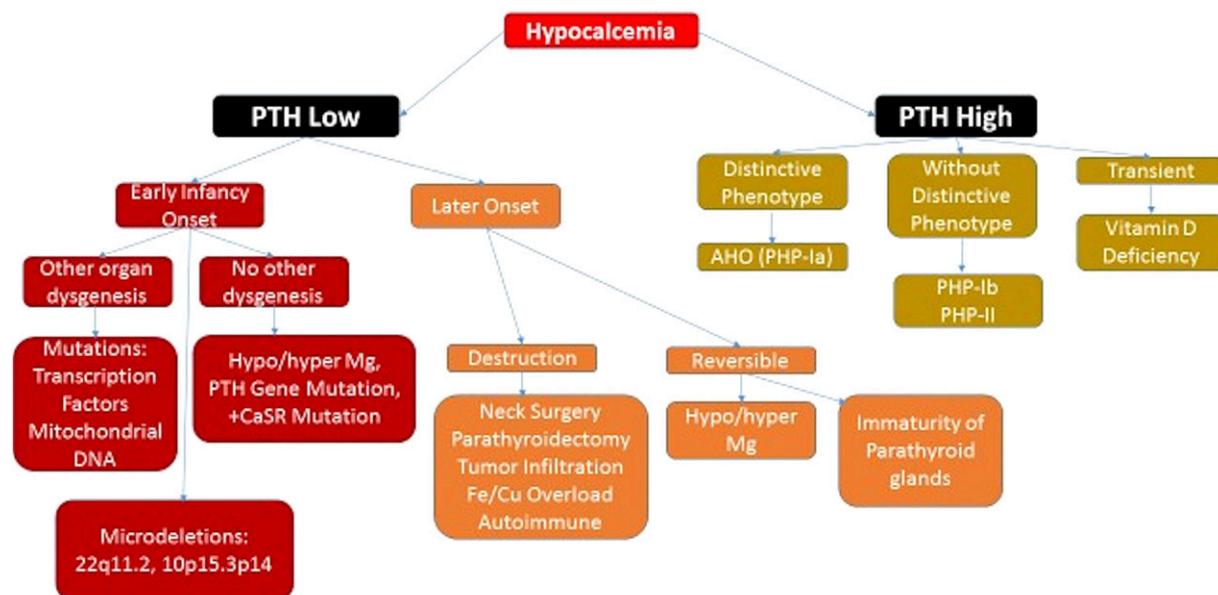


Figure 3. Differential diagnosis flow diagram for hypocalcemia. AHO=Albright hereditary osteodystrophy, CaSR=calcium-sensing receptor, Cu=copper, Fe=iron, Mg=magnesium, PHP= pseudohypoparathyroidism, PTH=parathyroid hormone.

heart and palate. (15) Microdeletions may occur in non-nuclear DNA. For example, mitochondrial DNA deletions resulting in the Kearns-Sayer syndrome are also associated with hypoparathyroidism, although the specific mechanism is not identified. (16)

Acquired hypoparathyroidism may be due to iatrogenic and noniatrogenic causes: intentional surgical removal of all parathyroid tissue for the treatment of parathyroid hyperplasia or accidental destruction, as during thyroidectomy or tumor resection. The treatment of chronic anemia diseases such as thalassemia with repeated blood transfusions can result in iron overload of multiple organs, including the parathyroids, if concomitant iron chelation therapy is not provided.

Noniatrogenic causes can be subdivided into 3 categories: transient, infiltrative, and destructive. Maternal hypercalcemia during pregnancy suppresses parathyroid gland development, but neonates recover within months after delivery. (17) Another reversible cause of hypoparathyroidism is due to abnormal concentrations of magnesium (both hypo- and hypermagnesemia). Metals such as copper in patients with poorly treated Wilson disease accumulate in the parathyroid glands, causing loss of function. This may be reversible with treatment. (18)

Neck tumors and granulomatous diseases may invade the parathyroids. Progressive destruction of the glands occurs in the polyglandular autoimmune syndrome type I that also includes chronic mucocutaneous candidiasis (nails, mouth, intestine, vagina) and adrenal failure. The source of this

disease is generally attributed to a dysfunctional product of the *AIRE* (autoimmune regulator) gene, although other genes may contribute. (19) Additional nongenetic factors leading to clinical presentation in this disease can be inferred by its delayed appearance but are unknown.

Treatment. Because circulating 1,25D (calcitriol) is produced in the kidneys under PTH stimulation of the 1- α -hydroxylase enzyme that converts 25-hydroxyvitamin D to calcitriol, concentrations are low in hypoparathyroidism. Without calcitriol, intestinal calcium absorption is diminished. Thus, the standard therapy historically has been to bypass this enzymatic block due to PTH deficiency and administer calcitriol in doses sufficient to maintain serum/blood calcium concentrations without inducing hypercalcemia/hypercalcemia. Synthetic PTH, which has been successfully used in the treatment of postmenopausal osteoporosis, could be considered as replacement for the endogenous deficit. However, concerns about bone tumor development in juvenile animals treated with PTH have raised questions about employing this product in children. In addition, as with insulin, it must be administered by injection several times a day whereas calcitriol is administered orally. Calcium must also be administered enterally either in food or as a supplement to provide the recommended daily intakes.

Pseudohypoparathyroidism

PHP is defined by a failure of PTH to correct hypocalcemia, that is, serum/blood calcium concentrations remain low despite elevated PTH concentrations.

Clinical Presentation. As in hypoparathyroidism, presenting symptoms are often attributable to hypocalcemia. Additional symptoms are specific to the cause and may include short stature, abnormal bones, and fetal or early neonatal death.

Clinical Signs. The usual diagnostic signs related to hypocalcemia, such as the Chvostek, may be elicited. Short stature, obesity, round face, and shortened metacarpals and metatarsals (Fig 4) can be found in Albright hereditary osteodystrophy. The laboratory findings in PHP are generally similar to those seen in patients with hypoparathyroidism, with the exception of a subgroup that features elevated alkaline phosphatase.

Causes. Almost all causes of PHP are genetic disorders (Fig 3). They can be distinguished on the basis of physical appearance, the level of unresponsiveness to PTH, and the identity of the dysfunctional gene. The genetics of these autosomal dominant diseases are complex and include mutations and epigenetic changes, primarily lack of appropriate methylation. There is parental imprinting such that inheritance of the defective allele from only the mother results in the disease.

Ironically, loss-of-function mutations in the PTH receptor (*PTHr1*) are not associated with PHP. They do present with skeletal changes of either advanced ossification in the recessively transmitted and lethal Blomstrand chondrodysplasia or skeletal maturation delay with normal calcium values in Eiken syndrome. (20)

The disorders can be categorized by their (lack of) renal responsiveness to exogenously administered PTH. In PHP type I, patients fail to increase urinary cAMP or phosphate excretion after a dose of PTH. There are several variants. Type Ia is also known as Albright hereditary osteodystrophy. The cause is lack of adequate expression of the α subunit of the G-protein that is responsible for PTH signal transduction. (8) The gene is located on chromosome 20, and the mutated allele is inherited from the mother only. (21) In PHP Ib, the biochemical profile is the same but there is no phenotype correlation. No gene mutation has been identified, but methylation defects in *GNAS* exon 1A of the same gene have been described. (22) More rarely, PHP Ib is attributed to reduced expression of *STX16*, a gene located in proximity to the α -G subunit gene that may regulate *GNAS* α methylation. (23) PHP Ib is also tissue-specific. The imprinting is restricted primarily to the kidney. Thus, PTH-induced osteoblast stimulation can result in a rise in serum alkaline phosphatase values.

PHP type II, like type Ib, is restricted to findings in the kidney and does not share the phenotype of PHP Ia. Unlike in PHP Ib, there is cAMP responsiveness to a dose of PTH



Figure 4. Hand and radiograph in child with pseudohypoparathyroidism Ia documents shortened metacarpals in the fourth and fifth digits.

but no increase in urinary phosphate. Thus, the defect occurs post-PTH receptor and its associated G-protein as a failure to respond to the cAMP messenger. Its cause remains unknown. Patients with vitamin D deficiency, with or without the bony manifestations of rickets, can appear to be resistant to PTH in that PTH concentrations may be elevated appropriately for the degree of hypocalcemia but serum phosphate concentrations are also elevated, as found in PHP. (24) In rickets due to vitamin D disorders, PTH typically induces phosphaturia, resulting in low serum phosphate concentrations. Correction of the vitamin D disorder also corrects the PHP.

Treatment. As with hypoparathyroidism, the mainstay of therapy for PHP is calcitriol together with an oral source of calcium. The dose of calcitriol can begin at 20 ng/kg per day, followed by titration every 3 days to achieve the desired ionized calcium range. Careful follow-up assessment of blood and urine calcium concentrations is necessary to provide sufficient medication without causing hypercalcemia/hypercalciuria complications.

HYPERPARATHYROIDISM

Because PTH responds to serum calcium concentrations, assessment of calcium is critical for determining the cause. In conditions of high calcium values, the parathyroid glands should decrease production and release of PTH, resulting in low serum values. If serum calcium and PTH concentrations are concomitantly high, this is termed most commonly as primary hyperparathyroidism. Appropriately elevated PTH values in response to low calcium concentrations is termed secondary hyperparathyroidism and indicates normal parathyroid gland responsiveness. Tertiary hyperparathyroidism is a term reserved for end-stage renal disease after renal transplant when the mass of parathyroid tissue produced during renal failure fails to respond normally to the serum calcium signal. Table 1 lists laboratory values according to type of hyperparathyroidism.

This section focuses on primary hyperparathyroidism and includes brief discussions of secondary and tertiary

hyperparathyroidism in addition to addressing common genetic syndromes producing primary hyperparathyroidism.

Primary Hyperparathyroidism

Symptoms and Signs. Primary hyperparathyroidism presents with hypercalcemia. Symptoms include abdominal pain, constipation, nausea and vomiting, flank pain, hematuria, polyuria, and changes in mentation progressing to stupor and coma. Manifestations may be subtle and can include fatigue, depression, and hypertension-related headache. Signs include weakness, loss of reflexes, bradycardia, and band keratopathy. Primary hyperparathyroidism may also present with bone disease characterized by generalized demineralization and subperiosteal resorption. With prolonged disease, cysts with a hemorrhagic component, known as brown tumors, may be found on radiography. These resolve upon reduction of PTH concentrations. (25)

Differential Diagnosis (Table 2). The differential diagnosis for primary hyperparathyroidism encompasses benign and potentially lethal causes, including sporadically occurring parathyroid adenomas or hyperplasia and diseases associated with specific known gene mutations (Fig 5).

Inherited loss-of-function mutations in both alleles of the CaSR gene result in a potentially lethal form of hyperparathyroidism known as neonatal severe primary hyperparathyroidism. This presents in the first 6 months after birth with polyuria, dehydration, failure to thrive, and hypertonemia. Survivors may have poor developmental outcomes. (26) Serum PTH and calcium concentrations are extremely high. If only 1 allele of this gene is affected, the infant has the more common and benign familial hypocalciuric hypercalcemia. This autosomal dominant mutation leads to a different “set point” for PTH suppression, with calcium values that are higher than the reference range and inappropriately normal or mildly elevated PTH values. The CaSR also operates in the renal tubule to modulate filtered calcium reabsorption. A decrease in the receptor’s function results in a decrease in urinary calcium, thus offering protection against the development of calcium stones. A urine calcium/creatinine clearance ratio of less than 0.01 is consistent with this

TABLE 1. **Hyperparathyroidism Laboratory Values**

TYPE OF HYPERPARATHYROIDISM	CALCIUM	PHOSPHORUS	CALCITRIOL	ALKALINE PHOSPHATASE	URINE CALCIUM/CREATININE RATIO
Primary	High	Low	High/Normal	High	High
Secondary	Normal/Low	Low	High/Normal	High	Low
Tertiary	High	Low	High/Normal	High	High

TABLE 2. Differential Diagnosis of Hyperparathyroidism

TYPE OF HYPERPARATHYROIDISM	DIFFERENTIAL DIAGNOSIS
Primary	Parathyroid adenoma Parathyroid hyperplasia
Secondary	Vitamin D deficiency 1- α -hydroxylase deficiency Chronic kidney disease Malabsorption Hereditary vitamin D-resistant rickets Malnutrition Intestinal disease Medications affecting vitamin D metabolism
Tertiary	Renal failure

diagnosis. Measuring the serum calcium of the parents may be helpful in confirming the clinical suspicion. (27) Gene analysis is helpful but not essential in most cases. Parathyroidectomy is not indicated for this disorder.

Later-onset hyperplasia of the glands or single adenomas may also cause primary hyperparathyroidism. Adenomas occur due to somatic mutations in τ cell, providing a survival advantage and leading to clonal proliferation. (25) In adults, these causes of hyperparathyroidism are relatively common. Most often, they are identified after hypercalcemia is detected on routine biochemical screening. However, the condition is much more likely to be suspected in a child when he or she presents with hypercalcemia-related symptoms. (28)

Parathyroid carcinoma can occur, but it is extremely rare, even in the adult population (less than 1% of those who have hyperparathyroidism), and is difficult to differentiate histologically from an adenoma. Affected patients present with very elevated PTH and calcium values, but this combination may also be seen with large bulky adenomas. (29) Other signs of carcinoma include a palpable neck mass and vocal hoarseness. The carcinoma has a 50% recurrence rate and may metastasize to the lungs. (25) A diagnosis of parathyroid carcinoma is based on the invasiveness of the lesion.

Genetic syndromes associated with primary hyperparathyroidism include multiple endocrine neoplasia (MEN)1,

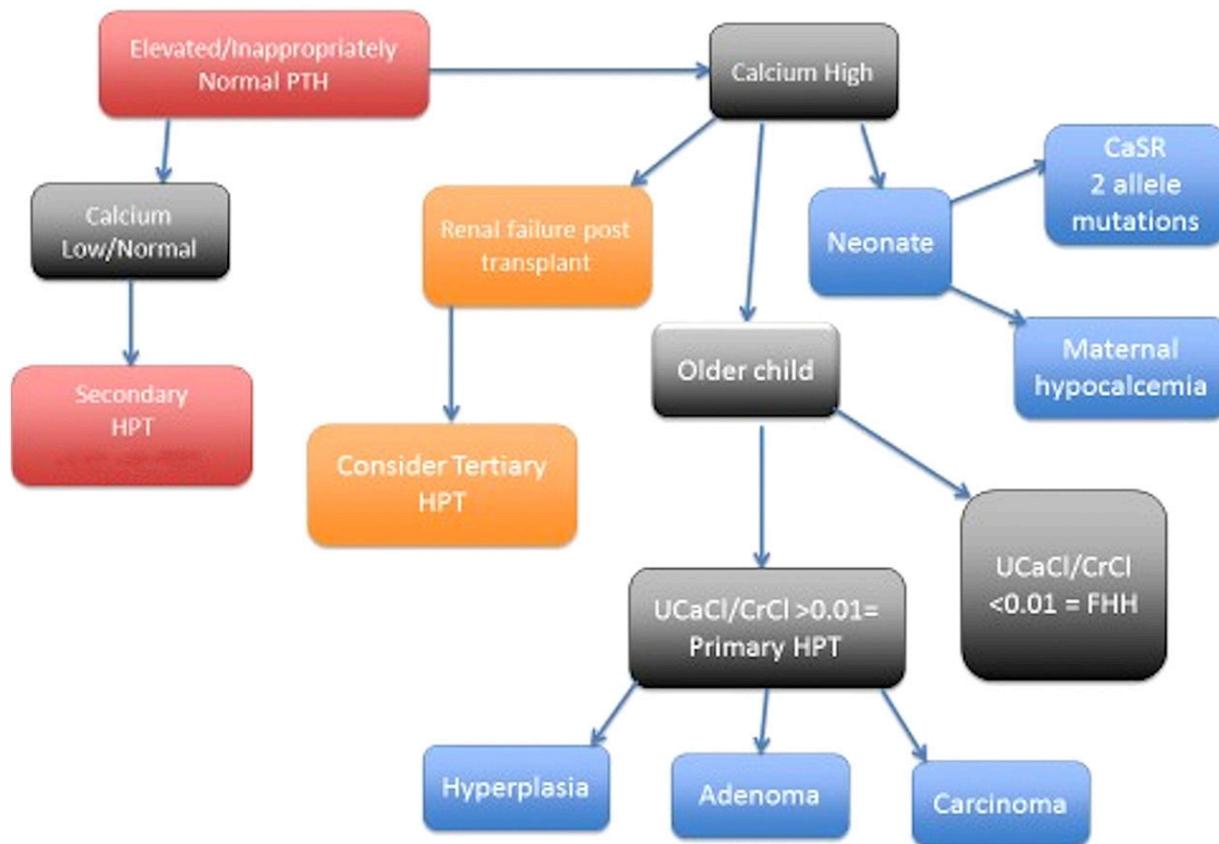


Figure 5. Differential diagnosis flow diagram for hyperparathyroidism. Ca=calcium, CaSR=calcium-sensing receptor, Cl=clearance, Cr=creatinine, FHH=familial hypocalciuric hypercalcemia, HPT=hyperparathyroidism, PTH=parathyroid hormone, U=urinary.

hyperparathyroidism jaw-tumor syndrome, and MEN2A. Active investigations of cases of nonsyndromic parathyroid adenomas or hyperplasia are likely to discover other genetic causes of primary hyperparathyroidism. (30)

MEN1 is characterized by 4-gland hyperplasia and is associated with pituitary tumors, insulinomas, or gastrinomas (the classic PPP for parathyroid, pituitary, and pancreas disease). It is due to mutations in the *MEN1* gene, which codes for a tumor suppressor product. Generally, MEN1 presents in the second to third decade, although it has been described in the first decade. Surgical treatment involves a total parathyroidectomy (because parathyroid disease tends to recur if fewer than 3 glands are removed) with a concurrent bilateral cervical thymectomy because of the risk for ectopic parathyroid and associated thymic carcinoid syndromes noted in this syndrome. (25)(31)

MEN2A describes a syndrome composed of medullary thyroid carcinoma, pheochromocytoma, and parathyroid adenoma(s). Parathyroid disease is less common than in MEN1 (90% versus <50%) and generally occurs later, beginning in the third decade, but has been reported in children. It is due to a mutation in the *RET* proto oncogene. (25) MEN2A surgical treatment involves only the enlarged gland, but consideration of the risk of associated medullary thyroid carcinoma may lead to more extensive surgery. (32)

Jaw-tumor syndrome, which is caused by a mutation in the *HRPT-2* gene leading to increased cell proliferation, has a higher risk for both parathyroid carcinoma and adenoma. Treatment should involve removal of tumor as well as involved muscles. (32) It is also associated with Wilms tumor and polycystic renal disease. (25) Due to the differences in management of these diseases, it is important to elicit a family history in pediatric patients with primary hyperparathyroidism and, in some circumstances, obtain the appropriate genetic testing.

Evaluation. The hallmark laboratory findings of primary hyperparathyroidism are an elevated serum calcium concentration in the presence of an elevated or inappropriately normal range PTH value (Table 1). Normally, high calcium levels suppress PTH. This differentiates primary from secondary hyperparathyroidism, which is characterized by an elevated PTH and normal or low serum calcium value. The initial laboratory evaluation should include ionized calcium, phosphorous, renal and liver function tests, electrolytes, magnesium, urinalysis, and urine calcium and creatinine. Because intact or functional PTH has a short half-life of a few minutes, the PTH should be assessed at the same time as the serum or blood calcium. Of note, pediatric patients (especially neonates) have higher phosphorous and alkaline phosphatase values compared to adult patients, so the use of age-appropriate reference ranges is important. If

PTH effects are fully manifest, the consequences of increased PTH-induced phosphaturia and bicarbonaturia will be reflected in lower-than-normal serum phosphate and bicarbonate values and a neutral or alkaline pH urine, ie, a renal tubular acidosis picture. PTH induction of bone turnover coupled with low phosphate results in increased serum bone-derived alkaline phosphatase. (28)(33) Also associated with hypercalcemia is a short QTc interval on electrocardiography that is generally considered less than 360 msec. (33) Perhaps because the disease is diagnosed after symptom onset, which is later in the disease course, the biochemical findings in primary hyperparathyroidism in children are more severe than in adults. (34)

Imaging to define the source of the hyperparathyroidism may include renal and neck ultrasonography and 99 mTc sestamibi scanning, which may be combined with single-photon emission computed tomography or ¹²³I technology. These techniques can localize adenomas in 80% to 90% of older children, but they are not as helpful with multigland hyperplasia. (25) Computed tomography scan (including 4-dimensional imaging) may also be used. Venous sampling, which looks for PTH gradients to localize a site of high PTH secretion, may be used in combination with imaging modalities to localize an ectopic abnormal gland. However, imaging in primary hyperparathyroidism is more likely to be used for surgical planning than for diagnosis. (32) Radiographs to confirm hyperparathyroid bone disease are not obtained routinely because the diagnosis is based on the biochemical profile; bone disease should resolve gradually after the PTH concentration normalizes.

Treatment. Parathyroid removal versus medical management is a source of debate for adult patients with primary hyperparathyroidism, but for patients younger than age 50 years, surgical removal is the generally agreed upon treatment of choice. (25) Surgery generally has a good prognosis. (26) Intraoperative PTH blood sampling can be used to assess surgical success and should demonstrate a decrease of at least 50%. For patients waiting to undergo surgery or those who are not surgical candidates, bisphosphonates and calcimimetics may be used. (35) In pediatrics, surgical excision is the treatment of choice. Calcimimetic use is rare and primarily is employed as a bridge to definitive surgical treatment. Calcimimetics act on the CaSRs, reducing the amount of PTH produced. They do not treat the underlying cause of hyperparathyroidism. Complications of surgery can include vocal cord paralysis and permanent hypoparathyroidism, but such complications occur in fewer than 1% to 4% of cases. Causes of surgical failure can be misdiagnosis of single versus multigland disease or parathyroid adenomas located in ectopic locations. (25)

Treatment for neonatal severe primary hyperparathyroidism is a 4-gland parathyroidectomy although, rarely, conservative measures including fluids, calciuretic agents, and bisphosphonates have been used with varying degrees of success. (36)

After surgical removal, more severe cases of primary hyperparathyroidism can manifest with hungry bone syndrome in which extraskelatal calcium is deposited into mineral-depleted bone. Hypocalcemia may result. Patients with very high alkaline phosphatase concentrations are more likely to develop postoperative hypocalcemia, and monitoring serum calcium beginning postoperatively and subsequently every few days after surgery is paramount. (25) Such patients may require intravenous calcium initially after surgery and the initiation of high doses of enteral calcium together with calcitriol. (33) Calcitriol is needed because PTH is a primary inducer of its production, and low PTH results in low calcitriol levels with diminished calcium absorption (Table 3). The need for supplemental calcium plus calcitriol often persists for 1 year after surgery.

Secondary Hyperparathyroidism

Symptoms. Secondary hyperparathyroidism is a state of appropriate elevation of PTH in response to a low or falling calcium stimulus (Fig 5). Symptoms relate to the hypocalcemia when not adequately corrected and were described previously.

Differential Diagnosis (Table 2). The causes of secondary hyperparathyroidism include inadequate calcium intake (isolated or part of a more general malnutrition), vitamin-D related disorders, malabsorption, and chronic kidney disease. (33)

Any problem in the vitamin D pathway may result in secondary hyperparathyroidism. The activated form of vitamin D, calcitriol (1,25D), increases intestinal calcium absorption. In vitamin D deficiency, inadequate substrate is available for calcitriol production. Vitamin D deficiency occurs because of lack of ultraviolet B radiation of skin to induce its production, inadequate intake, malabsorption, increased catabolism, or renal losses. End-organ resistance may also occur due to a diminished or nonfunctioning calcitriol receptor (known as the vitamin D receptor) that results in decreased calcium absorption. Also, inborn errors of the 1- α -vitamin D hydroxylase gene that result in non-functioning enzyme preclude calcitriol production.

The intermediary metabolite, 25-hydroxyvitamin D, is produced from vitamin D in the liver. Liver diseases and medications that stimulate hepatic catabolic pathways result in inadequate 25-hydroxyvitamin D production. Because the source of circulating hormonal calcitriol is the proximal renal tubule cell, end-stage kidney disease is associated with reduced plasma calcitriol concentrations.

In all of these situations, the sequence is the same: decreased calcium absorption is followed by a decrease in blood calcium concentration, which is corrected by an increase in PTH and ensuing bone calcium release. (25)

Evaluation. Biochemical evaluation of secondary hyperparathyroidism includes measurement of both total and ionized calcium, electrolytes, renal and liver function tests, serum phosphate, 25-hydroxyvitamin D, 1,25D, magnesium, and urine calcium and creatinine. Eliciting both a dietary and family history is important, and examination for signs of rickets is necessary.

Treatment. Treatment of these diseases may include calcium and vitamin D supplementation or administration of calcitriol (1,25D), depending on the cause. (25)

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism is rare in the pediatric population and occurs in the setting of persistent secondary hyperparathyroidism leading to parathyroid hyperplasia and subsequent autonomous PTH secretion (Fig 5). The most common situation is chronic kidney disease with uncontrolled secondary hyperparathyroidism. Patients may later develop tertiary hyperparathyroidism after renal transplant. Much like primary hyperparathyroidism, tertiary hyperparathyroidism presents with elevated serum calcium and elevated to inappropriately normal PTH (the history in this case is what differentiates the two entities). The incidence has been described as 0.5% to 5.6% of patients after renal transplant. Treatment may involve parathyroidectomy or, in some cases, calcimimetics. (37)

TABLE 3. Treatment of Hypocalcemia After Parathyroidectomy

MEDICATION	DOSE
Intravenous calcium	Bolus: 10% calcium gluconate (9.4 mL elemental calcium/mL) at a dose 0.5 mL/kg; watch for bradycardia Infusion: Calcium gluconate in 5% dextrose in ¼ normal saline to deliver 200 mg/kg salt in 24 hours (maximum 10 g)
Calcitriol (1,25 dihydroxyvitamin D)	0.01-0.05 μ g/kg per day, generally 0.1-3 μ g daily
Oral calcium	20-100 mg/kg elemental calcium daily divided into 3-4 doses

Summary

- On the basis of strong evidence, parathyroid hormone (PTH) is a peptide hormone that signals through a G-protein-coupled receptor (1) and is regulated primarily by changes in serum calcium. (3)
- On the basis of strong evidence, PTH acts through bone and kidney to raise serum calcium concentrations (6)(7) and lower serum phosphorus concentrations. (9)
- In hypoparathyroidism, low PTH levels result in low serum calcium, causing tetany and seizures. Clinical signs include Chvostek and Trousseau signs.
- Among the variety of causes for inherited hypoparathyroidism are specific gene defects, Barakat syndrome, Sanjad-Sakati syndrome, Kenny-Caffey syndrome, gain-of-function calcium-sensing receptor mutations, PTH gene mutations, and DiGeorge syndrome.
- On the basis of strong evidence, acquired hypoparathyroidism can result from surgical removal of the parathyroid glands, iron overload, magnesium disorders, Wilson disease, or autoimmune polyglandular syndrome type 1.
- Treatment of hypoparathyroidism is with calcium and activated vitamin D (calcitriol).
- On the basis of strong evidence, pseudohypoparathyroidism is characterized by low calcium despite high PTH concentrations, indicating resistance. Type Ia is caused by mutations in the *GNAS1* gene and is known as Albright hereditary osteodystrophy. Type Ib is caused by defects in *GNAS1* methylation and does not result in osteodystrophy. (8)
- In primary hyperparathyroidism, high serum calcium occurs with inappropriately high PTH levels.
- Clinical signs and symptoms of primary hyperparathyroidism include abdominal pain, constipation, nausea and vomiting, flank pain, hematuria, polyuria, stupor, coma, weakness, loss of reflexes, and bradycardia.
- Bone lesions called brown tumors can be seen on radiography.
- The broad differential diagnosis of primary hyperparathyroidism includes neonatal severe hyperparathyroidism and familial benign hypocalciuric hypercalcemia, both of which are caused by inactivating mutations of the calcium-sensing receptor.
- Parathyroid gland hyperplasia or parathyroid adenomas can cause PTH overproduction, which is common in adults but rarer in children.
- Parathyroid carcinoma is extremely rare and often fatal.
- Parathyroid adenomas can occur as part of a syndrome such as multiple endocrine neoplasia (MEN)1, hyperparathyroidism-jaw tumor syndrome, or MEN2A.
- Evaluation for hyperparathyroidism includes neck ultrasonography and sestamibi scan to detect and localize parathyroid adenomas.
- Treatment of hyperparathyroidism is surgical removal.
- If the PTH is elevated in response to hypocalcemia, this is termed secondary hyperparathyroidism.
- In tertiary hyperparathyroidism, hyperplastic parathyroid tissue loses responsiveness to calcium signaling.
- On the basis of strong evidence, secondary hyperparathyroidism is commonly seen with vitamin D deficiency. Chronic kidney disease can also cause secondary hyperparathyroidism, which can progress to tertiary hyperparathyroidism when it is long-standing. (25)

References for this article are at <http://pedsinreview.aappublications.org/content/37/12/524>.

PIR Quiz

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1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
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1. A 9-year-old boy presents to the emergency department with diffuse abdominal pain, nausea, and vomiting 2 hours after sustaining blunt trauma to the abdomen when he fell off his bike and hit the handlebars. Laboratory studies show elevated amylase, lipase, and hypocalcemia. He is diagnosed with acute pancreatitis and admitted for intravenous fluid hydration and management. Which of the following findings is expected to be seen as a result of the hypocalcemia?
 - A. Decreased QTc interval on electrocardiography.
 - B. Normal or slightly decreased phosphorus.
 - C. Positive Trousseau sign.
 - D. Rigidity of fingers (cannot be bent).
 - E. Hypophosphatemia.
2. You are called to the newborn nursery to evaluate a 3-day-old newborn who was noted by the nursing staff to have twitching of both hands. She was born at term via repeat cesarean delivery. On physical examination, she is mildly cyanotic and has a mild cleft palate. Heart examination documents a grade III/VI murmur. Laboratory studies reveal calcium of 6.9 mg/dL (1.73 mmol/L) and phosphorus of 9 mg/dL (2.91 mmol/L). The remainder of her electrolyte measurements are within normal limits, including normal serum glucose and sodium. Which of the following is the most likely cause of the clinical findings described in this patient?
 - A. DiGeorge syndrome.
 - B. Kenney-Caffey syndrome.
 - C. Maternal hypocalcemia during pregnancy.
 - D. Loss-of-function mutations in the parathyroid hormone (PTH) receptor.
 - E. Sanjad-Sakati syndrome.
3. A 9-month-old boy is brought to the clinic by his consanguineous parents for the evaluation of multiple subcutaneous nodules that have been present since birth but are increasing in size. Physical examination reveals multiple 5- to 7-mm hard subcutaneous nodules over the extremities. In addition, the patient is at greater than the 95th percentile for weight and less than the 25th percentile for height. He has a round face with short metacarpals and metatarsals. He is diagnosed with Albright hereditary osteodystrophy. Which of the following best describes the pathophysiology of the pseudohypoparathyroidism seen in patients who carry this diagnosis?
 - A. Absence of the parathyroid glands.
 - B. Decreased synthesis of PTH.
 - C. Normal PTH release but failure of tissues to respond.
 - D. Normal PTH synthesis but failure to release it.
 - E. Synthesis of defective PTH.
4. A 17-year-old girl presents with polyuria, nausea, vomiting, abdominal pain, and fatigue. Laboratory studies reveal calcium of 12 mg/dL (3 mmol/L), phosphorus of 2.1 mg/dL (0.68 mmol/L), and urine calcium/creatinine ratio of 2.2. Which of the following is the most appropriate next serum study to order in this patient?
 - A. Calcium/creatinine ratio.
 - B. Cortisol.
 - C. Insulinlike growth factor 1.
 - D. PTH.
 - E. Thyrotropin.

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This journal-based CME activity is available through Dec. 31, 2018, however, credit will be recorded in the year in which the learner completes the quiz.

5. A 16-year-old girl presents with tetany and hypocalcemic seizure. Physical examination shows positive Trousseau and Chvostek signs. Laboratory studies document elevated serum PTH. You diagnose secondary hyperparathyroidism. Which of the following diagnoses may lead to secondary hyperparathyroidism?
- A. Chronic kidney disease.
 - B. Hypervitaminosis D.
 - C. Kearns-Sayer syndrome.
 - D. Multiple endocrine neoplasia (MEN)1.
 - E. Parathyroid adenoma.