BMJ Best Practice

seudohypoparathyroidis

Straight to the point of care

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Summary

Pseudohypoparathyroidism results from resistance to the actions of parathyroid hormone (PTH) produced by a loss of G-protein-mediated signaling.

Different types are distinguished by the presence or absence of a characteristic skeletal phenotype, the responsiveness to PTH, the underlying mutations, and the inheritance pattern.

Manifests clinically with hypocalcemia, hyperphosphatemia, and elevated PTH levels.

Some patients have associated endocrinopathies. Hypothyroidism is the most common, but hypogonadism is also seen.

The mainstay of treatment is the normalization of calcium and phosphate levels using calcium supplementation, vitamin D, and thiazide diuretics. Associated endocrinopathies, if present, are treated with hormone replacement.

The underlying signaling defects are incurable.

Definition

Pseudohypoparathyroidism (PHP) results from an insensitivity of target tissues to the biologic actions of parathyroid hormone (PTH). It is caused by genetic mutations in the PTH signaling pathway.[1] [2] The disease manifests clinically with hypocalcemia, high PTH levels, and hyperphosphatemia. The disease may be symptomatic or asymptomatic. The diverse presentations relate to tissue specificity of expression, splice variations, and carrier status. Some forms of the disease are associated with a characteristic skeletal phenotype of short stature, stocky habitus, obesity, round face, dental hypoplasia, brachymetacarpals, brachymetatarsals, and soft-tissue calcification/ossification referred to as Albright hereditary osteodystrophy.

Epidemiology

Pseudohypoparathyroidism (PHP) is extremely rare. One study collected data from randomly selected departments of pediatrics, internal medicine, neurology, and endocrinology throughout Japan. A total of 203 patients were diagnosed with PHP in 1997, providing an estimated prevalence of 0.34 cases of PHP per 100,000 inhabitants in Japan. These numbers are likely to be an underestimate given the wide range of presentations of PHP.[9] One 2011 National Patient Registry review in Denmark identified 60 patients, a prevalence of 1.1 cases per 100,000 inhabitants.[10] Based on expert opinion, type Ia is the most common form. The ratio of women to men is approximately 2:1.[9] [10]

Etiology

Pseudohypoparathyroidism (PHP) occurs as a result of mutations in the downstream signaling cascade of parathyroid hormone (PTH)/PTH-related peptide receptor (PTHrP1). All mutations identified to date affect GNAS, the gene coding for the guanine nucleotide-binding protein (G-protein) Gs-alpha.[11] [12] [13] However, the causative mutation is not known for all forms of PHP. Gs-alpha gene (positioned on chromosome 20q13.3 at the GNAS locus) transcription is affected by genomic imprinting, an epigenetic (non-DNA -sequence determined) phenomenon, leading to aberrant or inadequate expression of Gs-alpha. Imprinting of a gene allows a cell to express only one allele, most commonly maternal origin, but paternal inheritance has also been described. These parent-of-origin metabolic effects are due to preferential expression from the maternal allele in a small number of tissues.[14] Ineffective silencing or methylation of GNAS genes may also result in the findings of PHP. Tissues involved in the parent-of-origin metabolic effects of Gs-alpha mutation are not known completely. The small number of affected tissues helps to explain the unique presentation of these patients. The etiology for obesity has been suggested to be the result of reduced energy expenditure from an imprinted Gs-alpha mutation in the paraventricular nucleus of the hypothalamus.[15] The type of PHP depends on the GNAS mutation, the imprinted tissue, and the inheritance pattern.

- Type Ia is caused by heterozygous loss-of-function mutations in Gs-alpha, inherited from the mother in humans and other mammals.[16] [17] [18] [19] [20] This reduction of G-protein-coupled signaling may result in lack of function of PTH, thyroid-stimulating hormone (TSH), gonadotropins, and growth hormone-releasing hormone. A characteristic skeletal phenotype, including short stature, stocky habitus, obesity, round face, dental hypoplasia, brachymetacarpals, brachymetatarsals, and soft-tissue calcification/ossification also results. It is referred to as Albright hereditary osteodystrophy.
- Type Ib is caused by less-severe sporadic or autosomal dominant mutations at GNAS locus, resulting in reduced expression of Gs-alpha, affecting PTH-sensitive tissues (mostly the kidney), and sometimes TSH-sensitive tissues (the thyroid gland). Other tissues are spared, so there are no morphologic abnormalities.
- Type Ic is typically associated with normal Gs-alpha activity and absence of GNAS mutations. However, mutations in the GNAS carboxy terminus have been detected in a subgroup of type Ic patients.[7] The phenotype of type Ic is similar to that of type Ia, with generalized hormone resistance and Albright hereditary osteodystrophy. The cyclic adenosine monophosphate (cAMP) response is blunted in type Ic, suggesting that there is a defect in the cAMP synthesis and breakdown cycle.
- Type II is caused by as-yet unidentified loss-of-function mutations without a mutation of the coding exons of Gs-alpha. The phenotype of type II is milder, with normal morphology and selective PTH resistance. The cAMP response to PTH is preserved in type II PHP, suggesting that the defect is located downstream of cAMP.[21]

Pseudopseudohypoparathyroidism is caused by the same mutations as type Ia and Ib PHP, but the mutations are inherited from the father rather than from the mother. Paternal inheritance produces no hormone resistance, but the characteristic skeletal phenotype still occurs. The reason for this is that Gs-alpha is primarily expressed from the maternal allele in the kidney. If the maternal allele has a nonfunctioning mutation, Gs-alpha-mediated function will be lost in the target tissues, causing PHP. However, if the paternal allele carries the mutation, Gs-alpha-mediated function will be preserved in the target tissues.[22] [23] [24] [25] Because the tissues affected by the characteristic skeletal phenotype require both alleles to be fully functional, these abnormalities are seen in some types of PHP and in patients with pseudo-PHP.

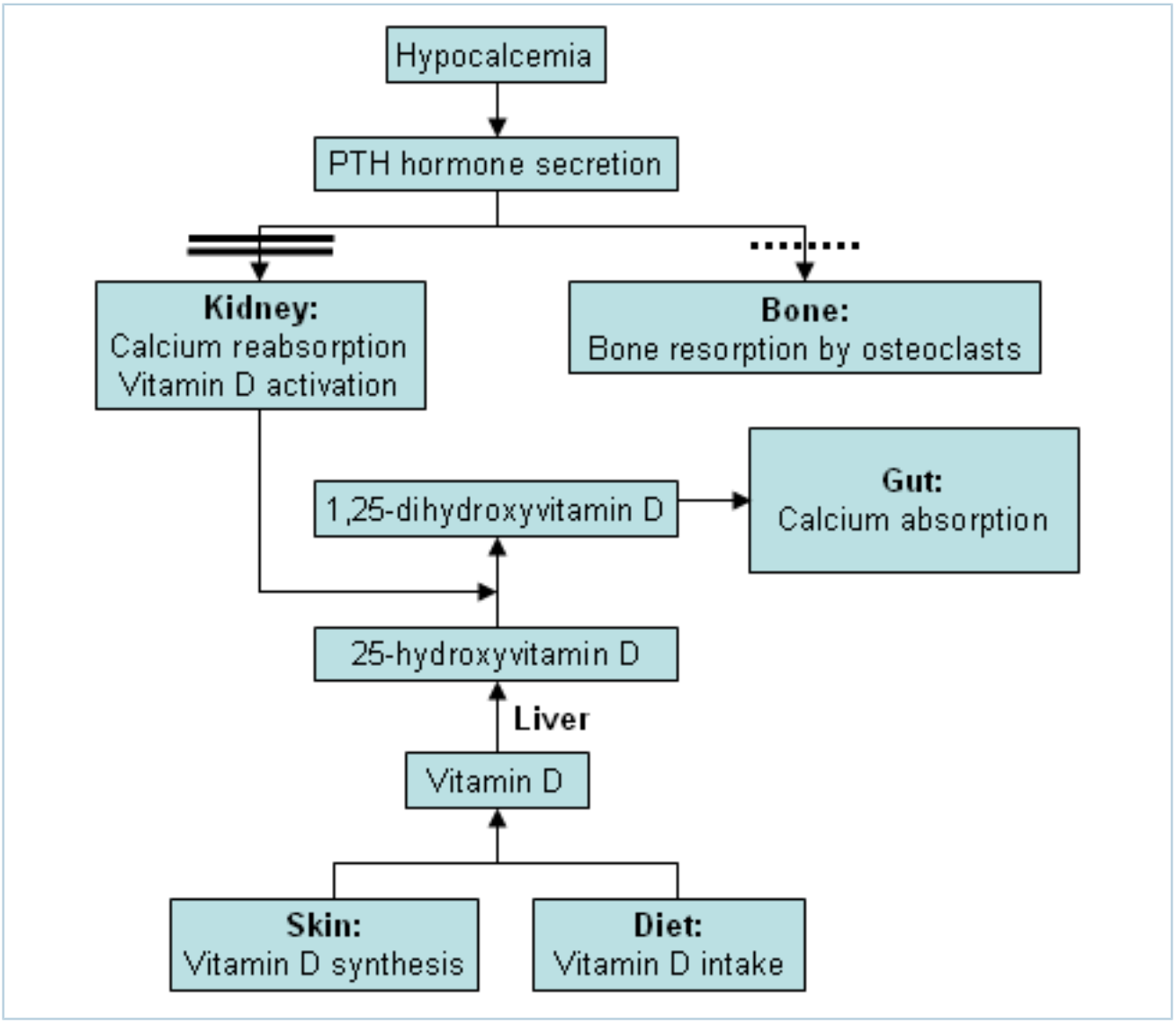
Pathophysiology

Parathyroid hormone (PTH) is primarily involved in calcium homeostasis. It is released from the parathyroid gland when a calcium receptor perceives decreased ionized calcium. PTH liberates calcium from bone, increases intestinal calcium absorption by promoting the synthesis and activation of vitamin D, and promotes calcium reabsorption and phosphate excretion in the kidneys. Binding of PTH or PTH-related peptide (PTHrP), a protein important for growth, to its receptor is followed by a cascade of events that are mediated by G proteins. Once the ligand binds to its receptor, the G-protein is activated and stimulates the synthesis of the second messenger, cyclic adenosine monophosphate (cAMP). Defects in cAMP signaling may result in metabolic, skeletal, or higher mental function abnormalities due to the broad distribution of this signaling system. The most common defects observed in PHP are PTH resistance (producing hypocalcemia), thyroid-stimulating hormone resistance (producing hypothyroidism), and the characteristic skeletal phenotype (Albright hereditary osteodystrophy). PTH resistance results in hypocalcemia. PTH levels become chronically elevated because the hypocalcemia and hyperphosphatemia continue to stimulate PTH production, which in turn is unable to restore calcium levels.

Many patients have chronic asymptomatic hypocalcemia, but symptoms of hypersensitivity of nerve and muscle, paresthesias, twitching, anxiety, and ECG abnormalities (QT prolongation) can occur. If calcium levels are not corrected in patients with symptomatic hypocalcemia, cardiac arrhythmia and death can occur.

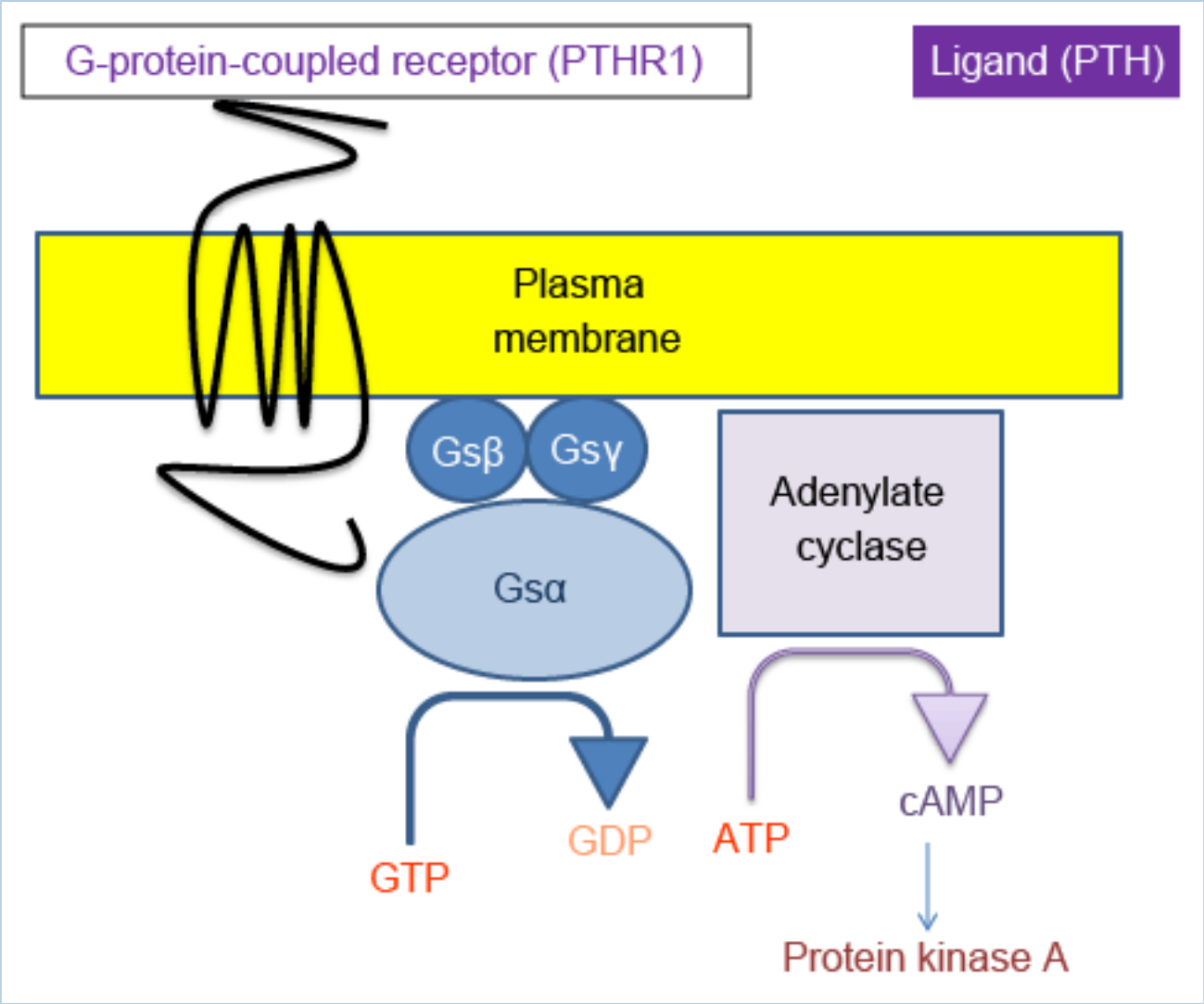
PTH resistance also leads to hyperphosphatemia, which stimulates PTH secretion in an effort to lower phosphate levels. Hyperphosphatemia leads to the increased formation of calcium phosphate in extraskeletal sites. Calcium phosphate can be deposited in the kidney (causing nephrolithiasis), the brain (causing calcification of the basal ganglia), the skin (causing subdermal calcification and ossification), and the eye (causing cataracts).

The characteristic skeletal phenotype is not related to PTH sensitivity. It occurs because of the crucial role of Gs-alpha signaling in the growth, differentiation, and structure of these tissues.



Overview of regulation of serum calcium. The double lines and dashed line indicate the defects in PTH signaling seen in PHP. The defect in the kidney response is more pronounced

Created at the BMJ Evidence Centre based on author information



The signaling cascade of parathyroid hormone

From the collection of Kent Wehmeier, University of Florida Jacksonville

Classification

Types of pseudohypoparathyroidism (PHP) based on clinical features, parathyroid hormone (PTH) responsiveness, and genotype[3] [4] [5]

Type Ia:

- Caused by heterozygous loss-of-function mutations upstream or within the GNAS locus, where the 13 exon gene encodes the stimulatory guanine nucleotide-binding protein (G-protein) alpha subunit, Gs-alpha
- Associated Albright hereditary osteodystrophy
- Decreased response to exogenous PTH as measured by urine cyclic adenosine monophosphate (cAMP) and urine phosphorus
- Serum calcium is low

- Hormone resistance is generalized, affecting hormones that rely on Gs-alpha signaling, such as PTH/PTH-related peptide (PTHrP), thyroid-stimulating hormone (TSH), gonadotropins, and growth hormone-releasing hormone
- Autosomal dominant inheritance; linked to maternal allele.

Type Ib:

- Caused by mutations in GNAS resulting in disruption of imprinting control elements
- Decreased Gs-alpha transcription in certain tissues where the gene transcript is derived from the maternal allele
- No significant change in activity of Gs-alpha is detected
- Hormone resistance is limited to PTH activity in the renal cortex
- No associated skeletal phenotype
- Decreased response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is low
- Hormone resistance is limited to PTH target tissue; however, there are an increasing number of cases associated with TSH resistance
- Inheritance may be sporadic or familial autosomal dominant.

Type Ic:

- Normal Gs-alpha activity together with the absence of GNAS mutations are the hallmarks of type Ic.[6] However, two nonsense and two missense mutations in the GNAS carboxy terminus have been detected in a few type Ic patients[6] [7] [8]
- Associated Albright hereditary osteodystrophy
- Decreased response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is low
- Hormone resistance is generalized (affecting any hormone that relies on Gs-alpha signaling)
- Inheritance similar to type Ia (i.e., autosomal dominant, linked to maternal allele).

Type II:

- Underlying genetic mutation is unknown
- No associated skeletal phenotype
- Complex response to exogenous PTH; urine phosphorus response is decreased but urine cAMP response is normal
- Serum calcium is low
- Hormone resistance is limited to PTH target tissue
- Inheritance is unknown.

Pseudopseudohypoparathyroidism:

- Caused by mutations in GNAS
- Associated Albright hereditary osteodystrophy
- Normal response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is normal
- No hormone resistance
- Autosomal dominant inheritance, linked to paternal allele.

Case history

Case history #1

A 12-year-old girl presents with short stature. She provides a history of muscle cramps and knots in her skin, and is obese with developmental delay. On exam she has a round face, hard subcutaneous nodules, shortened 3rd and 4th fingers bilaterally, and poor dental development.

Approach

Pseudohypoparathyroidism (PHP) is a rare condition, and referral to a specialized center should be considered. One 2018 international consensus statement and one 2020 review provides recommendations for diagnosis and management of PHP.[1] [2] Patients may be asymptomatic or present with symptoms and signs of hypocalcemia. In addition, patients with types Ia and Ic PHP have the characteristic skeletal phenotype of Albright hereditary osteodystrophy and often present with short stature. Subcutaneous calcification has been reported in the neonatal period.[29] A proportion of patients may have concurrent hypothyroidism. The different forms of PHP are distinguished by using a combination of clinical features, measurement of the response of urinary cyclic adenosine monophosphate (cAMP) and phosphate to exogenous parathyroid hormone (PTH) stimulation, and genetic testing.

Types Ia and Ic PHP have an autosomal dominant mode of inheritance.[26] Type Ib is usually sporadic, although familial cases have been reported.[27] [28]

The inheritance of type II PHP is unknown, but it has been hypothesized that type II PHP may be an acquired defect secondary to vitamin D deficiency.[6]

PTH resistance

PTH resistance produces hypocalcemia and hyperphosphatemia, which produce distinct clinical features. Hypocalcemia does not always manifest at birth but tends to occur between 3 and 8 years of age. Mild hypocalcemia is often asymptomatic. Some patients may report muscle cramps. Severe hypocalcemia is a medical emergency, and it is important to be alert for the key symptoms and signs. Paresthesias affecting the lips, fingers, or toes are common early symptoms. Severe hypocalcemia can cause muscle twitches, spasm, or tetany. If spasms affect laryngeal smooth muscle, the patient may develop life-threatening stridor. The patient may report lethargy or anxiety. If left untreated, patients can develop confusion, convulsions, or a fatal cardiac arrhythmia. PHP may also be a cause of paroxysmal dyskinesias (involuntary intermittent movement disorders).[30] Subtle signs such as brittle nails, dry hair, or calcification of the pinna of the ears may also be seen.

Hypocalcemia produces two key clinical signs.

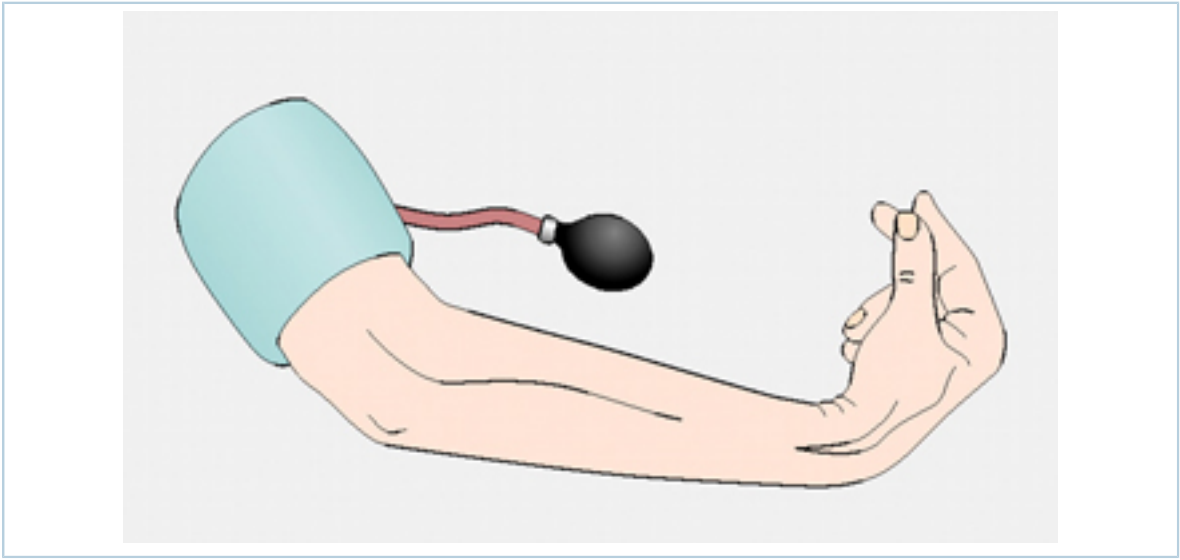
- Chvostek sign is elicited by tapping a finger on the facial nerve in front of the tragus of the ear with the mouth slightly opened. Twitching of the ipsilateral facial muscles is considered positive and is a sign of hypersensitivity of the nerve fibers.

Ask the patient to relax his facial nerves. Next, stand directly in front of him and tap the facial nerve either just anterior to the earlobe or below the zygomatic arch and the corner of the mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.

Eliciting Chvostek sign

Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

- Trousseau sign is elicited by inflating a blood pressure cuff placed over the brachial artery to 20 mmHg above systolic for 5 minutes. The distal ischemia produces tetany of the hand with flexion at the metacarpophalangeal joints and extension at the interphalangeal joints. The more rapid the response, the lower the serum calcium.



Eliciting Trousseau sign

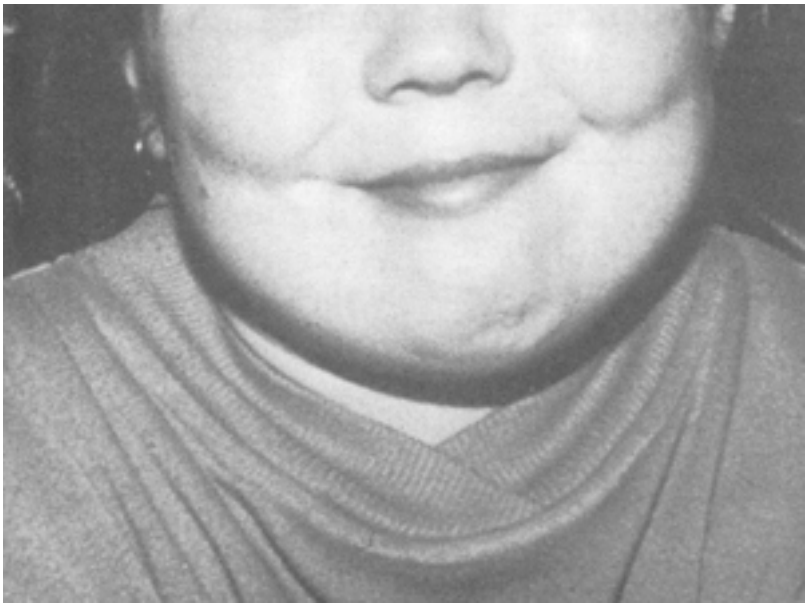
Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

Hyperphosphatemia produces an increase in the deposition of calcium phosphate in extraskeletal tissues. Calcium phosphate stones can form in the kidney, producing nephrolithiasis. Calcium phosphate deposition in the brain produces basal ganglia calcification, a classic computed tomographic (CT) finding of PHP. Calcium phosphate deposition in the skin produces subdermal calcification and ossification. Calcium phosphate deposition in the eye can cause cataracts. Routine ophthalmologic exam is required in all patients to identify cataract formation.

Albright hereditary osteodystrophy

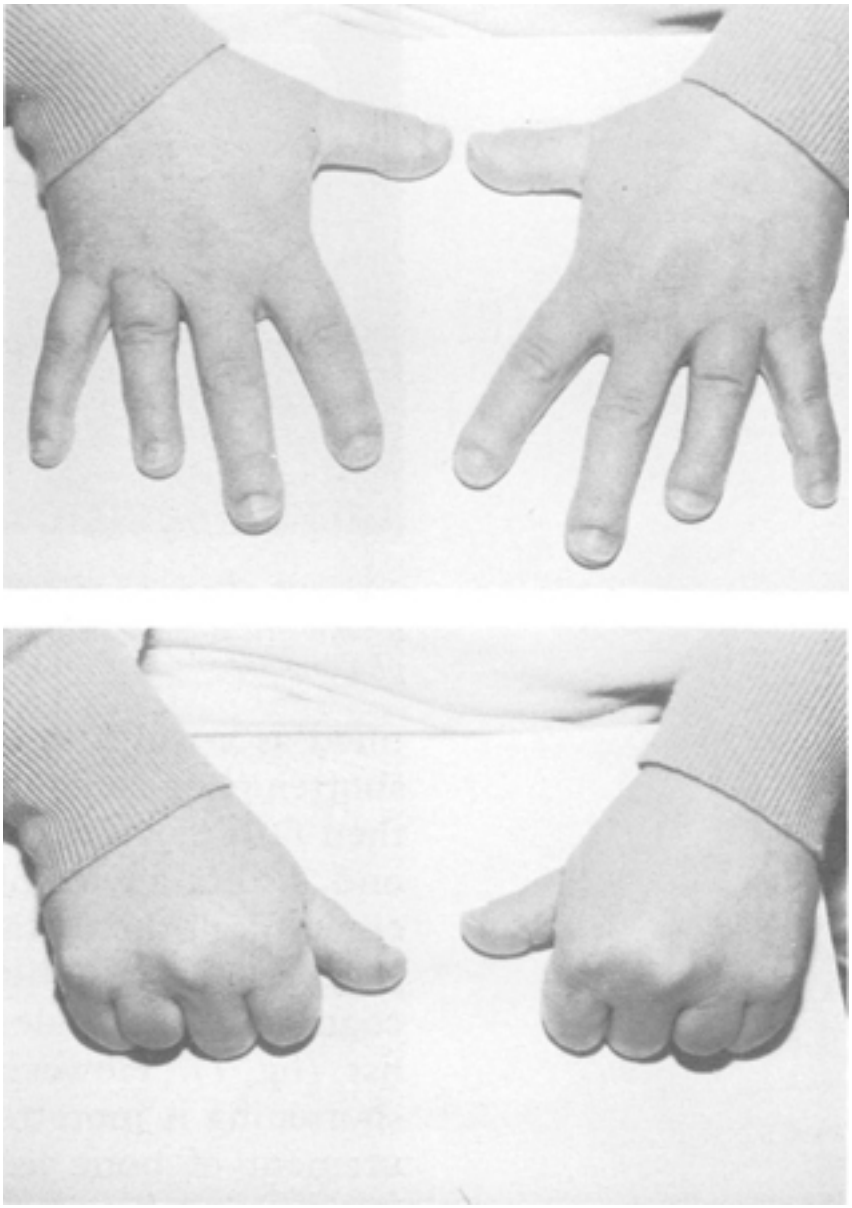
PHP types Ia and Ic are associated with Albright hereditary osteodystrophy, which has a characteristic skeletal phenotype. These characteristics include short stature (height $<10^{th}$ percentile), stocky habitus, round face, dental hypoplasia, brachymetacarpals, and brachymetatarsals. Most patients have associated intellectual disability and obesity. The most useful diagnostic sign is metacarpal shortening, classically affecting III, IV, and V metacarpals, which produces dimpling over the knuckles.[31]

Other congenital disorders may have a similar phenotype and can be difficult to distinguish.[32] However, these patients do not have any demonstrable defects in PTH signaling or function.



Child with Albright hereditary osteodystrophy showing a round face and a short nose with a flat nasal bridge

Wilson LC, Trembath RC. J Med Genet. 1994 Oct;31(10):779-84



Hands of an adult with Albright hereditary osteodystrophy showing shortening of the IV metacarpal and distal phalanges, and knuckle dimples in the clenched fists

Wilson LC, Trembath RC. J Med Genet. 1994 Oct;31(10):779-84

Other endocrine abnormalities and associations

The most common associated endocrine dysfunction is hypothyroidism, produced by decreased responsiveness to thyroid-stimulating hormone (TSH). The clinical features of hypothyroidism are nonspecific and include weakness, lethargy, cold sensitivity, constipation, weight gain, depression, menstrual irregularity, myalgia, dry or coarse skin, eyelid edema, thick tongue, coarse hair, facial edema, and bradycardia. Hypothyroidism can be seen in any patient with type Ia or Ic disease, and possibly in type Ib disease, too.

Other endocrine dysfunctions are rare and are seen in type Ia or Ic disease. These include gonadotropin and possibly growth hormone-releasing hormone (GHRH) resistance. Gonadotropin resistance usually manifests with delayed puberty or infertility. GHRH resistance manifests with features of growth hormone deficiency.

Sporadic cases of Chiari type 1 anomaly, cholesterol gallstones, psychosis, and osteosclerosis have been reported.[33] [34] [35] [36]

Initial tests

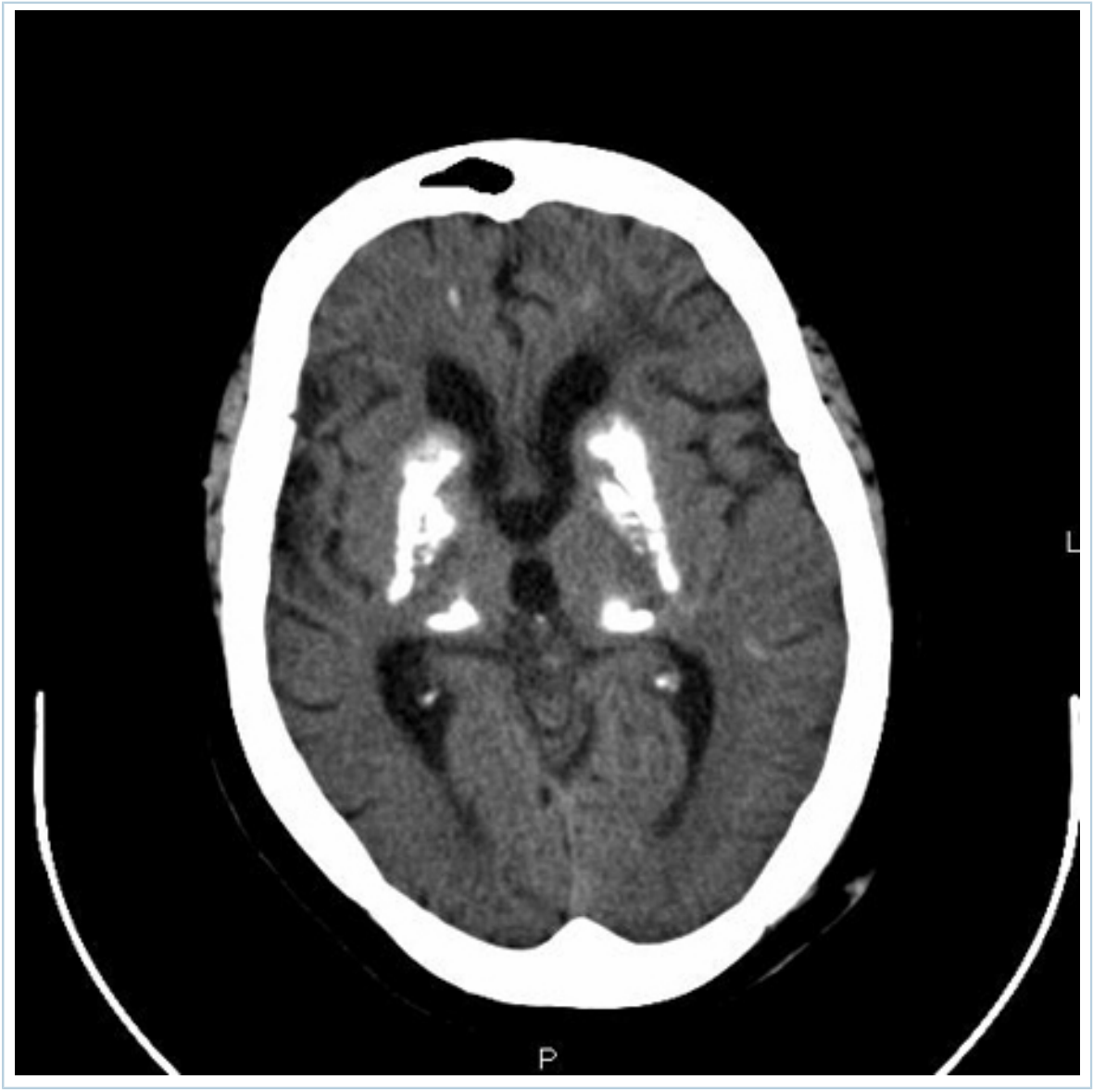
Serum calcium (total and ionized), phosphate, and PTH levels should be measured in all patients in whom the diagnosis is suspected. A serum creatinine is also required to aid in the interpretation of calcium and phosphate levels. Hypocalcemia and hyperphosphatemia associated with elevated PTH concentration and normal 25-hydroxyvitamin D levels strongly suggest a diagnosis of PHP. However, some patients may have normal calcium, phosphate, and PTH levels.

Other tests are performed to exclude other common causes of hypocalcemia. Serum magnesium levels should be measured to exclude hypomagnesemia, which can reduce PTH secretion and action. Levels of 25-hydroxyvitamin D should be measured to exclude vitamin D deficiency and osteomalacia.

Subsequent tests

Imaging

- In patients with the characteristic skeletal phenotype of Albright hereditary osteodystrophy, plain radiographs of the hands will reveal metacarpal shortening.[37]
- CT scanning of the brain may reveal calcification of the basal ganglia. It is not required for diagnosis, and is usually performed to exclude other causes of paresthesias and confusion.
- Dual-energy x-ray absorptiometry (DXA) bone-density scanning is required in patients with fractures. Bone loss can occur in any form of PHP due to preserved sensitivity of bone to PTH, but it is usually only significant in patients with low sex steroid levels as a result of associated gonadotropin resistance. Some researchers have suggested that in patients with PHP type Ia, regional bone density is normal while total bone density is elevated.[38]



CT findings of severe basal ganglia calcification in a patient with pseudohypoparathyroidism

From the collection of Kent Wehmeier, University of Florida Jacksonville

Response to exogenous PTH

- The response to exogenous human PTH (hPTH) is evaluated to distinguish the different subtypes of PHP. It is also the only way to establish the diagnosis of PHP in patients with inconclusive results on initial testing.
- The patient is taken off calcium supplements and fasted overnight. At 6 a.m., the patient begins to drink 250 mL fluid every hour until 12 noon. Two control urine specimens for measurement of cAMP, creatinine, phosphate, and calcium are collected before 9 a.m. Subcutaneous synthetic hPTH is given at 9 a.m., and urine is collected every half an hour for measurement of urinary cAMP and phosphorus. Serum samples are collected at 9 a.m. and 11 a.m. for measurement of creatinine, cAMP, 1,25-dihydroxyvitamin D, and phosphorus. The test is concluded at 12 noon.
- Normal subjects show a 10-fold to 20-fold increase in urinary cAMP excretion and a 20% to 30% increase in phosphate excretion regardless of the serum calcium concentration. The cAMP and phosphate response are both decreased in patients with type Ia, Ib, or Ic PHP. Patients with type II PHP have a decreased phosphate response, but the cAMP response is preserved. Patients with pseudopseudohypoparathyroidism will have a normal cAMP and phosphate response.

Genetic testing

- Mutational analysis of the GNAS gene (the gene that codes for the guanine nucleotide-binding protein Gs-alpha) is available through several clinical laboratories. This will reveal known causative mutations of type Ia, type Ib, and pseudopseudohypoparathyroidism.[4] [39] [40] [41] [42] [43] The causes of type Ic and type II are unknown.
- If there are existing genetic test results, do not perform repeat testing unless there is uncertainty about the existing result, e.g., the result is inconsistent with the patient's clinical presentation or the test methodology has changed.[44]

Other endocrine tests

- Type Ia or Ic can have generalized hormone resistance; thyroid function tests (free thyroxine, TSH) should be performed early because thyroid dysfunction is the most common associated endocrine dysfunction seen in these patients.
- Evaluation of the gonadotropin axis (follicle-stimulating hormone, luteinizing hormone, estradiol, or testosterone) and the GHRH-growth hormone axis (growth hormone, insulin-like growth factor-1) should also be considered in all patients with suspected types Ia and Ic PHP, or who have symptoms of delayed puberty or infertility.

Distinguishing PHP clinical subtypes

Using a combination of clinical features, hormone resistance, diagnostic tests, and genetic screening, the different subtypes of PHP can be distinguished.[3] [4] [6]

	Type Ia	Type Ib	Type Ic	Type II	Pseudo-PHP
AHO	yes	no	yes	no	yes
Calcium level	low	low	low	low	normal
PTH level	high	high	high	high	normal
Response to exogenous PTH	↓urine cAMP ↓urine phosphorus	↓urine cAMP ↓urine phosphorus	↓urine cAMP ↓urine phosphorus	normal urine cAMP ↓urine phosphorus	normalurine cAMP normalurine phosphorus
GNAS gene mutations	maternal inactivating mutations	imprinting dysregulation	few inactivating mutations reported	none	paternal inactivating mutations
Hormone resistance	multiple: PTH, TSH, Gn, GHRH	PTH, TSH	multiple: PTH, TSH, Gn	PTH only	none

AHO: Albright hereditary osteodystrophy; Pseudo-PHP: pseudopseudohypoparathyroidism; cAMP: cyclic adenosine monophosphate; PTH: parathyroid hormone; TSH: thyroid stimulating hormone; Gn: gonadotropins; GHRH: growth hormone releasing hormone

Subtypes of pseudohypoparathyroidism

Created by Dr Emad Naem

History and exam

Key diagnostic factors

positive family history of PHP (common)

- Types Ia and Ic have an autosomal dominant mode of inheritance. Due to the poor reproductive capacity of people who have types Ia or Ic, little information is available regarding how frequently the mutation is passed on.[26]
- Type Ib is usually sporadic, although familial cases are reported.[27] [28]
- The inheritance of type II is unknown, but it has been hypothesized that it may be an acquired defect secondary to vitamin D deficiency.[6]

muscle cramp (common)

- Many patients with mild hypocalcemia are asymptomatic, but muscle cramp is the most common symptom encountered.

paresthesias (common)

- Affect the lips, fingers, or toes.
- A common early symptom of hypocalcemia.

muscle twitches (common)

- A sign of severe hypocalcemia.

positive Chvostek sign (common)

- Elicited by tapping a finger on the facial nerve in front of the tragus of the ear with the mouth slightly opened.
- Twitching of the ipsilateral facial muscles is considered positive and is a sign of hypersensitivity of the nerve fibers.
- Occurs in hypocalcemia but is not specific.

Ask the patient to relax his facial nerves. Next, stand directly in front of him and tap the facial nerve either just anterior to the earlobe or below the zygomatic arch and the corner of the mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.

Eliciting Chvostek sign

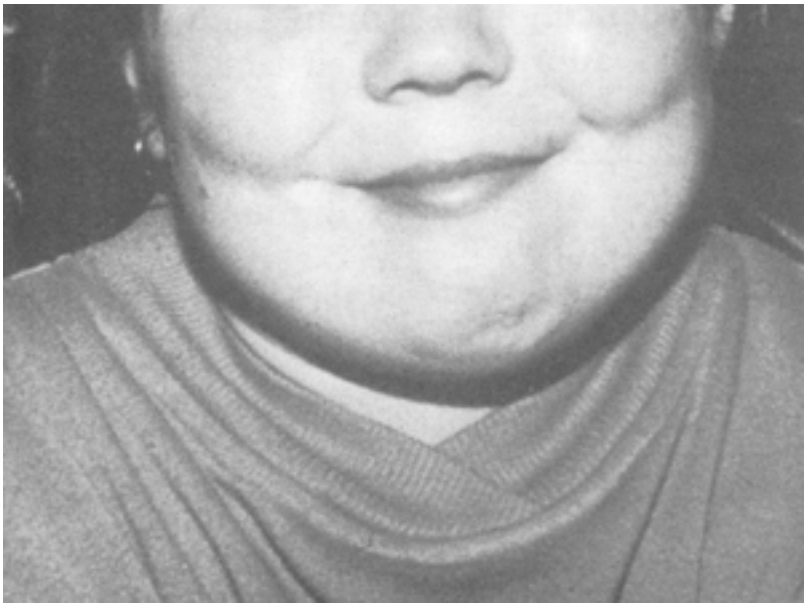
Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

intellectual disability (common)

- A key feature of PHP.

Albright hereditary osteodystrophy (common)

- Features include short stature (height <10th percentile), stocky habitus, round face, brachymetacarpals, brachymetatarsals, BMI 95th percentile or greater, and dental abnormalities.
- Dental abnormalities include enamel hypoplasia, absent or delayed tooth eruption, and short or blunted roots.



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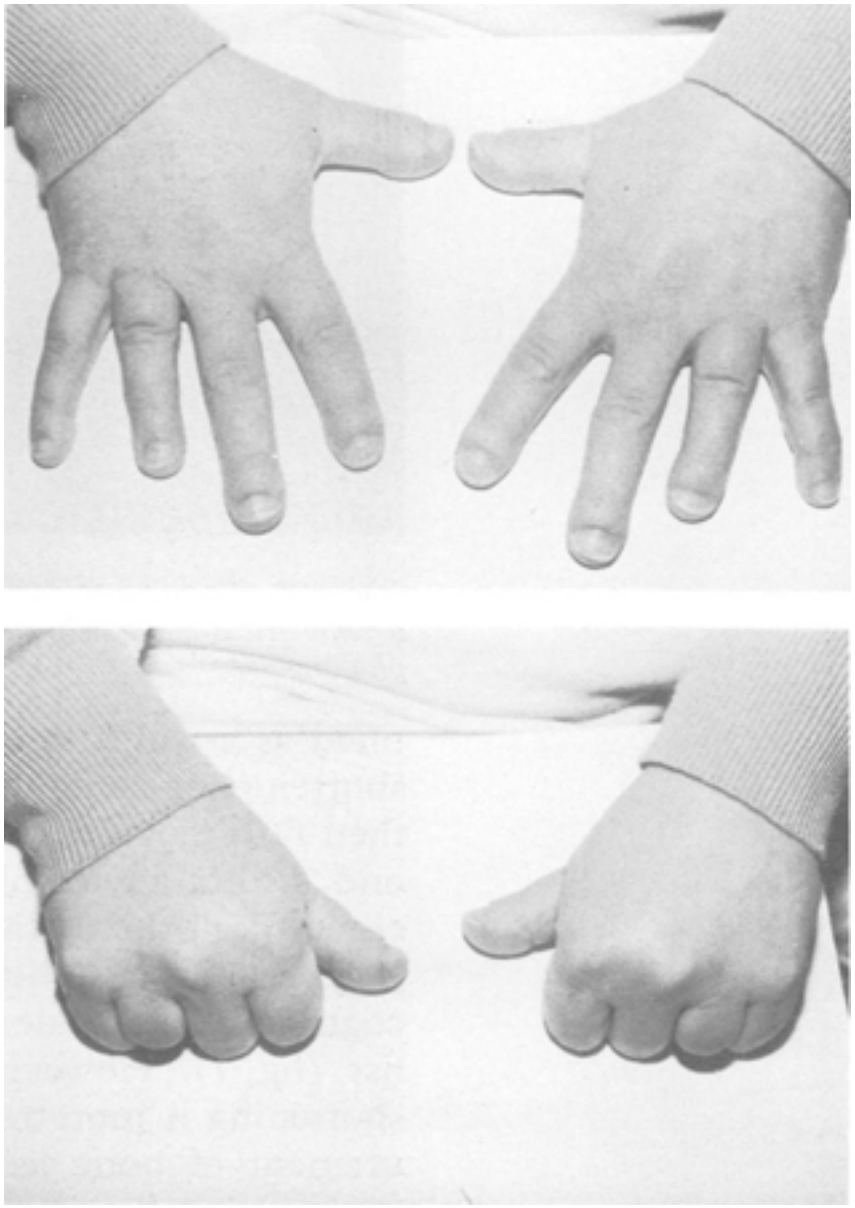


Hands of an adult with Albright hereditary osteodystrophy showing shortening of the IV metacarpal and distal phalanges, and knuckle dimples in the clenched fists

Wilson LC, Trembath RC. J Med Genet. 1994 Oct;31(10):779-84

muscle spasm (uncommon)

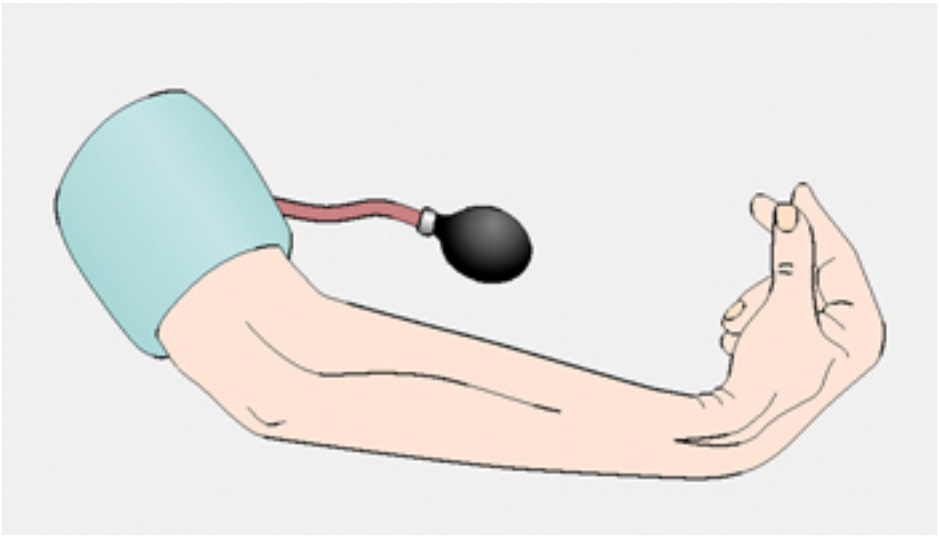
- A sign of severe hypocalcemia. If spasms affect laryngeal smooth muscle, the patient will develop life-threatening stridor.

tetany (uncommon)

- A late sign of severe hypocalcemia.

positive Trousseau sign (uncommon)

- Elicited by inflating a blood pressure cuff placed over the brachial artery to 20 mmHg above systolic for 5 minutes.
- The distal ischemia produces tetany of the hand with flexion at the metacarpophalangeal joints and extension at the interphalangeal joints.
- The more rapid the response, the lower the serum calcium.



Eliciting Trousseau sign

Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

Other diagnostic factors

lethargy (common)

- A nonspecific symptom that may reflect either hypocalcemia or hypothyroidism.

anxiety (common)

- A nonspecific symptom that can occur in hypocalcemia.

seizures (uncommon)

- Occurs in severe hypocalcemia.

paroxysmal dyskinesias (uncommon)

- PHP is a rare cause of paroxysmal dyskinesias (involuntary intermittent movement disorders).[30]

brittle nails (uncommon)

- A subtle sign of hypocalcemia.

dry hair (uncommon)

- A subtle sign of hypocalcemia.

subcutaneous calcification (uncommon)

- Calcification of the pinna of the ear or subdermal calcification/ossification occur as a consequence of calcium phosphate deposition, produced by hyperphosphatemia.[45]

cataracts (uncommon)

- A consequence of hyperphosphatemia, leading to calcium phosphate deposition in the eye.

features of hypothyroidism (uncommon)

- The clinical features of hypothyroidism include weakness, lethargy, cold sensitivity, constipation, weight gain, depression, menstrual irregularity, myalgia, dry or coarse skin, eyelid edema, thick tongue, coarse hair, facial edema, and bradycardia.

features of other hormone resistance (uncommon)

- Delayed puberty and infertility; commonly seen in patients with generalized hormone resistance due to resistance to the action of gonadotropins.

Chiari type 1 anomaly (uncommon)

- Sporadic cases of this congenital hindbrain abnormality have been reported.[33]

history of cholesterol gallstones (uncommon)

- Sporadic cases.[34]

features of psychosis (uncommon)

- Sporadic cases.[35]

Risk factors

Strong

positive family history of PHP

- Types Ia and Ic have an autosomal dominant mode of inheritance. Due to the poor reproductive capacity of people who have types Ia and Ic, little information is available regarding how frequently the mutation is passed on.
- [26]
- Type Ib is usually sporadic, although familial cases are reported.[27] [28]
- The inheritance of type II is unknown, but it has been hypothesized that type II PHP may be an acquired defect secondary to vitamin D deficiency.[6]

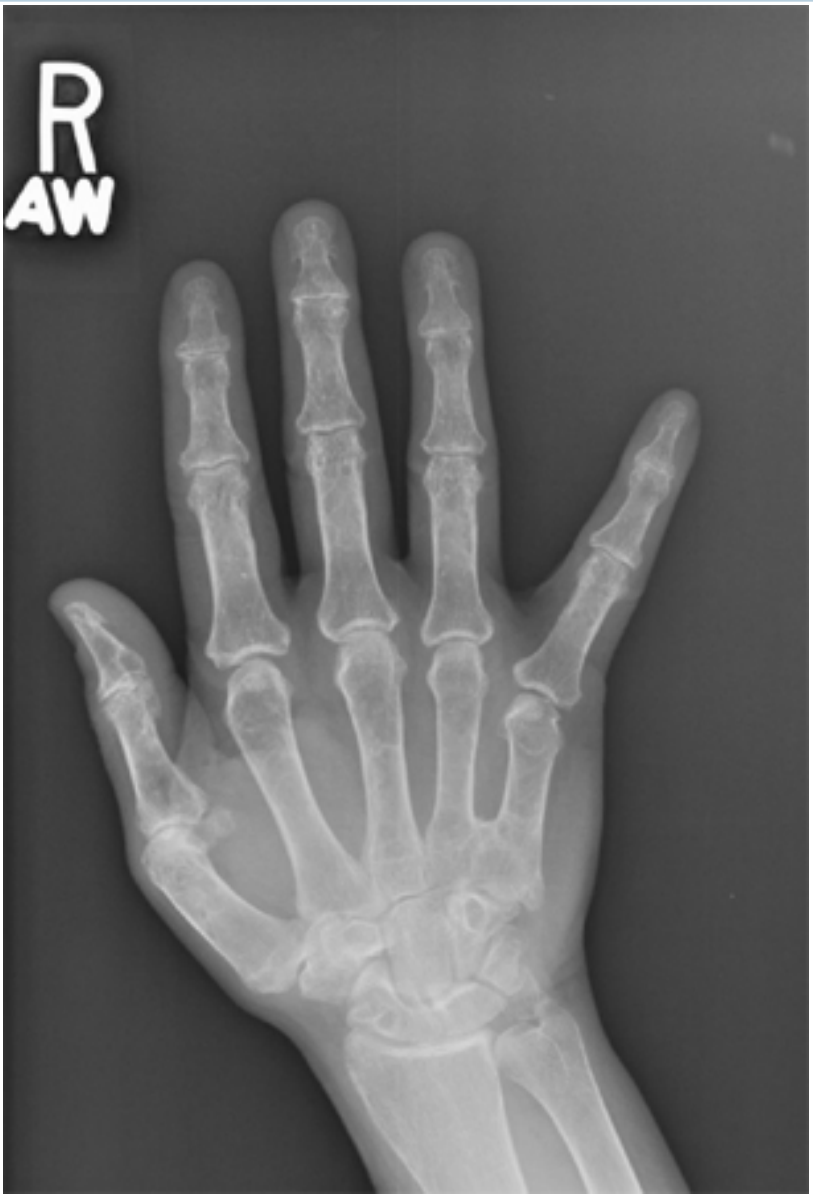
Tests

1st test to order

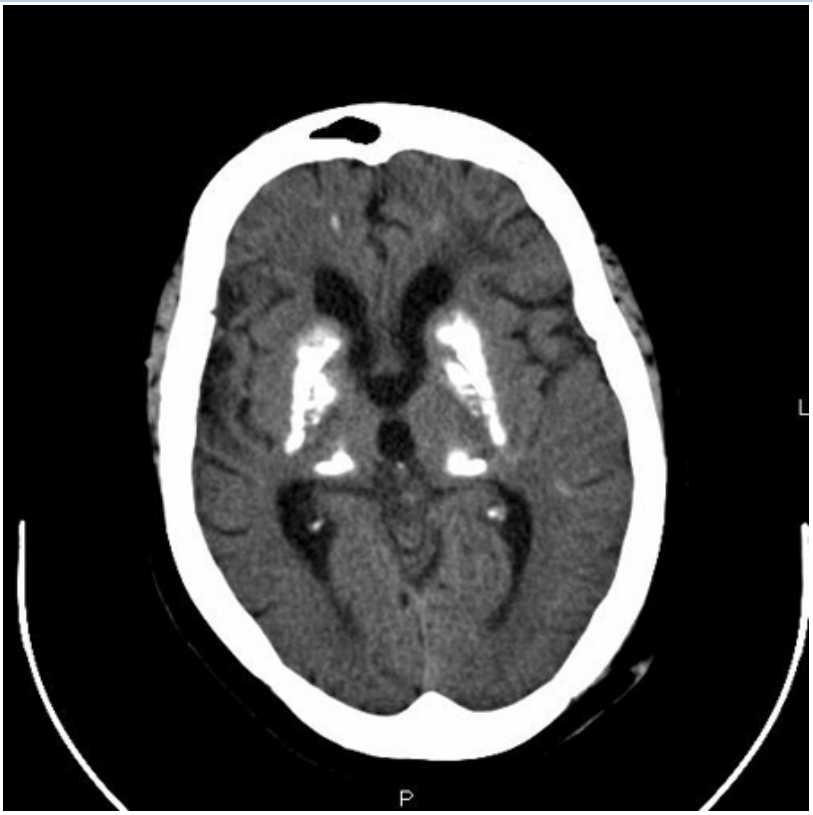
Test	Result
serum calcium • Should be considered in patients with symptoms suggestive of hypocalcemia (seizures, paresthesia, muscle cramps, prolonged QT interval), in patients with a positive family history, and in those with Albright hereditary osteodystrophy. • Ideally should be performed fasting. Ionized calcium is the preferred test because it accounts for factors such as pH and protein binding. • If total calcium is used, an albumin level should be determined. Adjusted calcium level can be calculated when the albumin level is abnormal and gives an estimate of what the calcium level would be if the albumin level were within the normal range. • Adjusted calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 x (4.0 - serum albumin [g/dL]), where 4.0 represents the average albumin level in g/dL. • Serum calcium is normal in pseudopseudohypoparathyroidism.	**typically low or may be normal**
serum phosphorus • Measured along with serum calcium. • Ideally should be performed fasted. • Serum phosphate is normal in pseudopseudohypoparathyroidism.	**typically elevated or may be normal**
serum PTH • Elevated PTH suggests pseudohypoparathyroidism (PHP). • Reduced PTH suggests hypoparathyroidism as the cause for hypocalcemia. • PTH levels can be normal in mild cases, and in pseudopseudohypoparathyroidism.	**typically elevated or may be normal**
serum creatinine • Necessary to interpret calcium and phosphorus values as appropriate or inappropriate. Secondary hyperparathyroidism due to chronic kidney disease should be suspected if hypocalcemia and hyperphosphatemia are associated with high PTH level and significant creatinine elevation.	**normal**
serum magnesium • A low level of magnesium needs to be corrected before interpreting PTH results.	**normal or low**
serum 25-hydroxyvitamin D • Usually normal in PHP. • Vitamin D deficiency can cause elevated PTH and hypocalcemia, and should be corrected before PHP is diagnosed.	**normal**
follicle-stimulating hormone • Evaluation of the gonadotropin axis, including follicle-stimulating hormone, should be considered in all patients with suspected type Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility. Resistance to follicle-stimulating hormone may be present.	**may be elevated**

Test	Result
luteinizing hormone • Evaluation of the gonadotropin axis, including luteinizing hormone, should be considered in all patients with suspected type Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility.	**may be elevated**
estradiol • Evaluation of the gonadotropin axis, including estradiol, should be considered in all patients with suspected type Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility.	**may be low**
testosterone • Evaluation of the gonadotropin axis, including testosterone, should be considered in all patients with suspected type Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility.	**may be low**
growth hormone • Evaluation of the growth hormone-releasing hormone-growth hormone axis should be considered in all patients with suspected type Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility.	**growth hormone deficiency may be detected**
insulin-like growth factor-1 • Evaluation of the growth hormone-releasing hormone-growth hormone axis, including insulin-like growth factor-1, should be considered in all patients with suspected types Ia and Ic PHP and in those who have symptoms of delayed puberty or infertility.	**may be low**

Other tests to consider

Test	Result
x-ray hands • Brachydactyly in Albright hereditary osteodystrophy is produced by relative shortening and widening of specific long bones in the hands, usually the III, IV, and V metacarpals, and the first distal phalanx.  *Hand radiograph suggestive of shortened IV and V metacarpals* *From the collection of Kent Wehmeier, University of Florida Jacksonville* • Findings may be asymmetric. • Madelung-like wrist deformity (MLD) has been reported in patients with PHP type Ib. MLD is characterized by marked chondrodysostosis, prominence of the lower end of the ulna, marked shortening and bowing of the radius, and palmar and ulnar deviation of the carpal bones.[46]	**metacarpal shortening**

Test	Result
ECG • The QT interval is rate-dependent. A corrected QT (QTc) of more than 0.44 seconds is pathologic and requires further evaluation. • Required in any patient who is symptomatic or who has significant hypocalcemia to evaluate myocardial irritability • A prolonged QT interval can be an early sign of an impending arrhythmia.	**normal or increased QT interval**
serum thyroid-stimulating hormone (TSH) • Type Ia or Ic disease can have generalized hormone resistance; thyroid function tests (free thyroxine, TSH) should be performed early because thyroid dysfunction is the most common associated endocrine dysfunction seen in these patients. • Should be collected in the morning. Serum TSH levels exhibit a diurnal variation, with the peak occurring during the night and the nadir, which approximates to 50% of the peak value, occurring between 10 a.m. and 4 p.m. The effect of this biological variation on thyroid function tests will be minimized if TSH and thyroid hormone measurements are performed in the morning.	**normal or elevated**
serum free thyroxine (T4) • Type Ia or Ic disease can have generalized hormone resistance; thyroid function tests (free T4, TSH) should be performed early because thyroid dysfunction is the most common associated endocrine dysfunction seen in these patients. • Should be collected in the morning.	**normal or reduced**
response to exogenous human PTH(1-34) • Findings of this test help to confirm the diagnosis in cases with equivocal results in other tests, and to distinguish the different subtypes of PHP.[4] • Types Ia, Ib, and Ic produce a decreased response of cyclic adenosine monophosphate (cAMP) and phosphorus. • Type II produces a decreased phosphorus response but a normal cAMP response. • Pseudopseudohypoparathyroidism produces a normal phosphorus and normal cAMP response.	**decreased response of urinary phosphate and/or cAMP**
dual-energy x-ray absorptiometry (DXA) bone-density scan • Required in patients with fractures. • Bone loss can occur in any form of PHP due to preserved sensitivity of bone to PTH, but is usually only significant in patients with low sex steroid levels as a result of concomitant gonadotropin resistance. • Rarely, osteosclerosis has occurred (high bone density).[36]	**decreased bone mass; Z-score may be normal or below -2**
CT head • Not required for diagnosis.	**basal ganglia calcifications**

Test	Result
 *CT findings of severe basal ganglia calcification in a patient with pseudohypoparathyroidism* *From the collection of Kent Wehmeier, University of Florida Jacksonville* • Usually performed to exclude other causes of seizures or confusion.	
mutation analysis of GNAS • Identifies mutations in GNAS (the gene that codes for the guanine nucleotide-binding protein Gs-alpha) that cause types Ia, Ib, and pseudopseudohypoparathyroidism. • If there are existing genetic test results, do not perform repeat testing unless there is uncertainty about the existing result, e.g., the result is inconsistent with the patient's clinical presentation or the test methodology has changed.[44]	**may or may not identify mutation**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Pseudopseudohypoparathyroidism	Patients have Albright hereditary osteodystrophy without symptoms or signs of PTH hormone resistance.	• Serum calcium and PTH are normal. • Normal response to exogenous PTH as measured by urine cyclic adenosine monophosphate and urine phosphorus. • Paternal inheritance of causative GNAS mutations (GNAS is the gene that codes for the guanine nucleotide-binding protein Gs-alpha).
Primary hypoparathyroidism	• History of prior thyroid gland surgery, multiple transfusions, or Wilson disease. • Morphologic features of DiGeorge syndrome may be present (hypertelorism, micrognathia, short philtrum with fish-mouth appearance, antimongoloid slant, telecanthus with short palpebral fissures). • Deafness or blindness suggestive of mitochondrial disease. • May be associated with intellectual disability and delayed development.	• Parathyroid hormone levels may be low. • Serum magnesium may be low or elevated.
Secondary hyperparathyroidism	• Patients may have chronic kidney disease with fatigue, anorexia, dyspnea, and edema. • Children with vitamin D deficiency may have signs of rickets.	• In people with renal insufficiency, serum creatinine is elevated, with elevated PTH levels produced by decreased calcium and decreased 1,25-dihydroxyvitamin D levels.
Vitamin D deficiency	• Symptoms and signs of rickets: hypotonia, bone pain and tenderness, muscle weakness, bow legs and knob knees, Harrison groove, pigeon deformity of the chest, kyphoscoliosis. Vitamin D deficiency rickets may mimic PHP in infants, causing elevated PTH level, hypocalcemia,	• Low 25-hydroxyvitamin D levels are diagnostic.

Condition	Differentiating signs / symptoms	Differentiating tests
	and hyperphosphatemia. Treatment with vitamin D will normalize these parameters.[47]	
Fanconi syndrome	• Causes include sickle cell disease or chemotherapy identified in the history.	• High urine calcium excretion without elevation of serum phosphate. • Generalized aminoaciduria and glycosuria. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Fluorosis	• Symptoms of bone pain.	• Serum phosphorus is low to normal. • Patients have increased bone density. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Osteopetrosis	• Family history of osteopetrosis is present. • The infantile form produces growth retardation, failure to thrive, and nasal stuffiness due to malformation of the mastoid and paranasal sinus. • Skull deformities can produce cranial nerve entrapment or hydrocephalus. • The adult form is milder and may be asymptomatic, or produce increased susceptibility to fractures. • Nerve damage produced by bone fractures can cause blindness, facial paralysis, or deafness.	• Serum phosphorus is low to normal. • Patients have abnormally high bone density. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Osteosclerosis	• No distinguishing clinical features.	• Serum phosphorus is low to normal. • Patients have abnormally high bone density. • The response of urinary cyclic adenosine monophosphate and

Condition	Differentiating signs / symptoms	Differentiating tests
		phosphate to human PTH is normal.
Familial brachydactyly	• Isolated abnormalities of the hand.	• X-ray reveals shortening of the middle phalanx of all digits. • Serum calcium and phosphorus are normal. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Prader-Willi syndrome	• Patients have poor muscle tone and hyperphagia with a constant feeling of hunger.	• Genetic testing identifies the causative mutations on chromosome 15. • Serum calcium and phosphate levels are normal. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Acrodysostosis	• Features of the head and face include brachycephaly, a hypoplastic "pug" nose, maxillary hypoplasia, an open mouth, and epicanthal folds.	• Serum calcium and phosphate levels are normal. • The response of urinary cyclic adenosine monophosphate and phosphate to human PTH is normal.
Turner syndrome	• Diagnostic morphologic features include low-set or malrotated ears, down-sloping eyes, ptosis or hooded eyes, and low posterior hairline. A high-arched palate is also seen.	• Karyotype reveals 10% or more of the cells with complete or partial loss of a sex chromosome.

Criteria

Types of pseudohypoparathyroidism (PHP) based on clinical features, parathyroid hormone (PTH) responsiveness, and genotype[2] [3] [4]

Type Ia:

- Caused by mutations in GNAS, the gene that codes for the guanine nucleotide-binding protein (G-protein) Gs-alpha
- Associated Albright hereditary osteodystrophy

- Decreased response to exogenous PTH as measured by urine cyclic adenosine monophosphate (cAMP) and urine phosphorus
- Serum calcium is low
- Hormone resistance is generalized (affecting any hormone that relies on Gs-alpha signaling)
- Autosomal dominant inheritance; linked to maternal allele.

Type Ib:

- Caused by mutations in GNAS
- No associated skeletal phenotype
- Decreased response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is low
- Hormone resistance is limited to PTH target tissue; however, there are an increasing number of cases associated with thyroid-stimulating hormone resistance
- Inheritance is sporadic.

Type Ic:

- Normal Gs-alpha activity together with the absence of GNAS mutations are the hallmarks of type Ic.[6] However, two nonsense and two missense mutations in the GNAS carboxy terminus have been detected in a few type Ic patients[6] [7] [8]
- Associated Albright hereditary osteodystrophy
- Decreased response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is low
- Hormone resistance is generalized (affecting any hormone that relies on Gs-alpha signaling)
- Inheritance similar to type Ia (i.e., autosomal dominant, linked to maternal allele).

Type II:

- Underlying genetic mutation is unknown
- No associated skeletal phenotype
- Complex response to exogenous PTH; urine phosphorus response is decreased but urine cAMP response is normal
- Serum calcium is low
- Hormone resistance is limited to PTH target tissue
- Inheritance is unknown.

Pseudopseudohypoparathyroidism:

- Caused by mutations in GNAS
- Associated Albright hereditary osteodystrophy
- Normal response to exogenous PTH as measured by urine cAMP and urine phosphorus
- Serum calcium is normal
- There is no hormone resistance
- Autosomal dominant inheritance, linked to paternal allele.

Approach

The underlying signaling defects are incurable. The main aim of management of parathyroid hormone (PTH) resistance is to maintain levels of calcium and phosphorus within the normal range while avoiding hypercalciuria.[1] [2] Symptomatic hypocalcemia is a medical emergency and requires prompt treatment. Asymptomatic hypocalcemia can be managed primarily with oral calcium supplements. Associated endocrinopathies are treated with hormone replacement. Treating patients with diminished mental function requires instructing appropriate caregivers to ensure proper administration of medication.

Patients with symptomatic hypocalcemia

Symptomatic hypocalcemia is an acute medical emergency, and intravenous calcium gluconate should be given as soon as possible. Calcium should be given in an infusion to reduce fluctuations in levels. ECG monitoring is required during the administration of intravenous calcium to detect calcium-induced cardiac conduction defects. If the response to intravenous calcium is inadequate, calcitriol (a vitamin D metabolite) can be added to improve calcium absorption from the gut; this is particularly beneficial in infants.[48] Patients with pseudohypoparathyroidism (PHP) do not usually have vitamin D deficiency, and care must be taken to avoid vitamin D overdosing. Calcitriol is preferred to cholecalciferol or ergocalciferol because PTH-mediated activation is not required, and calcitriol toxicity is easier to reverse as it has a short half-life and is not stored in adipose tissue.

The patient should be transitioned to oral calcium supplements once the acute symptoms have resolved.

Long-term management of hypocalcemia

This involves the reduction of extraskeletal calcification by achieving serum calcium goal at the lower limit of laboratory normal range, and normalization of serum phosphorus. Oral calcium supplements (e.g., calcium carbonate and calcium acetate) are preferred for maintaining a normal serum calcium. The advantage of these supplements is that they also act as phosphate binders and reduce the absorption of phosphate from the gut. They therefore allow calcium levels to be maintained without increasing the risk of extraskeletal calcification. Dietary sources of calcium also contain high levels of phosphate, so increasing calcium intake from this source increases the risk of extraskeletal calcification. Aluminum phosphate binders should be avoided.

Vitamin D enhances the absorption of calcium from the gut; calcitriol can be given to increase calcium levels if normalization of calcium levels is not achieved with calcium supplementation. Thiazide diuretics can reduce calcium loss through the kidney and can be added to further increase calcium levels.

Associated endocrinopathies

Associated endocrinopathies require treatment with hormone replacement. The most common is hypothyroidism, which requires long-term treatment with levothyroxine. In children with short stature, growth hormone therapy may be beneficial. Children with delayed maturation may require exogenous testosterone or estrogen. The onset of growth hormone deficiency in PHP type Ia is variable, making the time interval to treat short stature limited. Attempts to determine the etiology and best treatment regimen are ongoing. The effect of human growth hormone in this group has been studied and researchers demonstrated successful attainment of height velocity in prepubertal children.[49] In this small series only one child attained normal final height. The findings suggested the lack of sufficient growth hormone-releasing hormone effect as a major component of short stature.

For more information on the management of children with delayed maturation and those with growth hormone deficiency, please see Delayed puberty and Growth hormone deficiency in children .

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute		(summary)
symptomatic hypocalcemia		
	1st	intravenous calcium gluconate or calcium chloride + ECG monitoring

Ongoing		(summary)
asymptomatic hypocalcemia		
	1st	oral calcium supplements
	adjunct	calcitriol
	adjunct	thiazide diuretic
■ with hypothyroidism	plus	levothyroxine
■ children with short stature due to growth hormone deficiency	adjunct	growth hormone therapy
■ children with delayed puberty	adjunct	testosterone or estrogen

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

symptomatic hypocalcemia

1st **intravenous calcium gluconate or calcium chloride + ECG monitoring**

Primary options

» calcium gluconate

OR

» calcium chloride

» Symptomatic hypocalcemia is an acute medical emergency, and intravenous calcium gluconate or calcium chloride should be started as soon as possible.

» Calcium should be given in an infusion to reduce fluctuations in levels.

» ECG monitoring is required during the administration of intravenous calcium to detect calcium-induced cardiac conduction defects. Rapid administration may cause bradycardia, hypotension, and vasodilation. Infiltration of intravenous calcium may cause severe tissue necrosis and sloughing.

» Calcium levels should be monitored regularly.

» The patient should be transitioned to oral calcium supplements as soon as the acute symptoms have resolved.

» Consult local protocol for dosing and administration guidelines.

Ongoing

asymptomatic hypocalcemia

1st **oral calcium supplements**

Primary options

» calcium carbonate: children: 45-65 mg/kg/day orally given in 4 divided doses; adults: 1-2 g/day orally given in 3-4 divided doses
Dose expressed as elemental calcium.

OR

» calcium acetate: adults: 1-2 g/day orally given in 3-4 divided doses
Dose expressed as elemental calcium.

» Calcium carbonate and calcium acetate are preferred to dietary sources for maintaining a normal serum calcium.

» Dietary sources of calcium also contain high levels of phosphate, which increases the risk of extraskeletal calcification.

» Calcium carbonate and calcium acetate act as phosphate binders and reduce the absorption of phosphate from the gut. They can therefore lower serum phosphate levels and reduce the risk of extraskeletal calcification.

adjunct **calcitriol**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcitriol: children <1 year of age: consult specialist for guidance on dose; children 1-5 years of age: 0.25 to 0.75 micrograms orally once daily; children >5 years of age and adults: 0.25 micrograms orally once daily

» If the response to calcium supplements is inadequate, calcitriol (a vitamin D metabolite) can be added to improve calcium absorption from the gut.

» Patients with PHP do not have vitamin D deficiency, and care must be taken to avoid vitamin D overdosing.

» Toxicity is easier to reverse with calcitriol because it has a short half-life and is not stored in adipose tissue. Calcitriol is therefore preferred to cholecalciferol or ergocalciferol.

adjunct **thiazide diuretic**

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrochlorothiazide: children: 1-2 mg/kg/day orally given in 2 divided doses; adults: 12.5 mg orally once daily

» Thiazide diuretics reduce the urinary excretion of calcium and can be added to further increase calcium levels.

with hypothyroidism **plus** **levothyroxine**

Treatment recommended for ALL patients in selected patient group

Primary options

» levothyroxine: children: consult specialist for guidance on dose; adults: 1.7 micrograms/kg/day orally initially, increase by 12.5 to 25 micrograms/day increments every 2-4 weeks according to response

» Hypothyroidism is the most common associated endocrinopathy and requires lifelong treatment with levothyroxine.

children with short stature due to growth hormone deficiency **adjunct** **growth hormone therapy**

Treatment recommended for SOME patients in selected patient group

» Growth hormone therapy may be beneficial in children with short stature due to growth hormone deficiency.

» The onset of growth hormone deficiency in PHP type Ia is variable, making the time interval to treat short stature limited. Attempts to determine the etiology and best treatment regimen are ongoing. The effect of human growth hormone in this group has been studied and researchers demonstrated successful attainment of height velocity in prepubertal children.[49] In this small series only one child attained normal final height. The findings suggested the lack of sufficient growth hormone-releasing hormone effect as a major component of short stature. For more information on treatment of growth hormone deficiency, please see Growth hormone deficiency in children .

children with delayed puberty **adjunct** **testosterone or estrogen**

Treatment recommended for SOME patients in selected patient group

» Children with delayed maturation may require exogenous testosterone or estrogen. For more

Ongoing

information on treatment of delayed puberty, please see Delayed puberty .

Secondary prevention

Most complications can be prevented by meticulous management of oral calcium and vitamin D therapy to ensure that serum calcium and phosphate levels remain in the normal range. Adequate fluid intake is also important to help prevent nephrolithiasis.

If a patient with pseudohypoparathyroidism would like to conceive, preimplantation genetic diagnosis (PGD) should be considered to decrease and potentially eliminate the transmission of GNAS mutation to the fetus. PGD allows the selection of embryos without GNAS mutations for implantation.[58]

Patient discussions

Adherence to treatment is important and should be encouraged. Calcium should be taken in divided doses with food. Tight adherence to dietary guidelines regarding high calcium but low phosphorus intake is important. The dietary prescription needs to be tailored to the age of the patient, the severity of the calcium and phosphorus defects, and the ability to tolerate oral calcium.[55] [57] Patients should be encouraged to cease smoking.

If a patient with pseudohypoparathyroidism would like to conceive, preimplantation genetic diagnosis (PGD) should be considered to decrease and potentially eliminate the transmission of GNAS mutation to the fetus. PGD allows the selection of embryos without GNAS mutations for implantation.[58]

Monitoring

Monitoring

Patients with pseudohypoparathyroidism (PHP) require monitoring to ensure normalization of calcium and phosphate levels.[1] Calcium, phosphate, and 25-hydroxyvitamin D levels must be monitored regularly to avoid inadequate or excessive treatment. Calcium and phosphate metabolism changes during acute illness, growth spurts, and pregnancy, and the frequency of monitoring must be increased if any of these are present. The frequency of monitoring also depends on how quickly calcium and phosphorus goals are attained and the frequency of treatment failure. Albright hereditary osteodystrophy is associated with type Ia and Ic PHP, which are the forms most likely to be associated with hypothyroidism. If patients have Albright hereditary osteodystrophy and/or confirmed hypothyroidism, yearly evaluation of thyroid-stimulating hormone is required. In patients with fractures suspicious of osteopenia, bone-density scanning should be obtained. Patients with hypogonadism will also require regular monitoring of sex hormone levels. Regular ophthalmologic exams should be performed to detect cataract formation.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
tetany	**short term**	**medium**
Relaxation of muscle is an active process requiring calcium; hypocalcemia reduces the ability of muscle to relax, producing cramps, spasms, and ultimately tetany. Meticulous management of oral calcium and vitamin D is required to prevent this condition.		
ventricular tachycardia	**short term**	**low**
Repolarization of myocardium requires calcium. Hypocalcemia reduces the available calcium, resulting in prolongation of the QT interval, which can progress to ventricular tachycardia. Meticulous management of oral calcium and vitamin D is required to prevent this complication. Hypocalcemia can be exacerbated during acute illness or alkalosis, and the risk of ventricular tachycardia is therefore increased.		
primary hypothyroidism	**long term**	**high**
The most common associated endocrinopathy. Signaling of thyroid-stimulating hormone (TSH) occurs through G-proteins, and the loss of this second messenger results in primary hypothyroidism. Many cases can be identified by screening at birth. Affected patients will require long-term levothyroxine with yearly monitoring of TSH and thyroid hormone levels.		
bone loss	**long term**	**high**
Bone sensitivity to PTH is usually preserved, and elevated levels of PTH may lead to bone loss. The mainstay of prevention is to maintain a normal calcium level. Concomitant gonadotropin resistance in patients with PHP can lead to low levels of testosterone and estrogen, which can exacerbate bone loss. Hormone replacement is needed to prevent bone loss in these patients. [NIH Osteoporosis and Related Bone Diseases National Resource Center] (http://www.niams.nih.gov/Health_Info/Bone)		
cataracts	**long term**	**high**
Occur as a result of paradoxical deposition of calcium in the lens. Avoiding excess calcium replacement and lowering of phosphate to physiologic range are important to prevent extraskeletal calcium deposition. Routine ophthalmologic exam should be performed to identify cataracts.		
short stature	**long term**	**high**
Short stature occurs as part of Albright hereditary osteodystrophy, but can also occur due to defective growth hormone-releasing hormone signaling. Screening based on routine height and weight measurement should allow determination of inadequate growth. PTH-related protein, a crucial signal in linear growth, may also be affected by abnormalities of G-proteins. Little information is available regarding the use of growth hormone in these patients.[50]		
obesity	**long term**	**high**
Obesity is commonly seen. Age-appropriate counseling regarding appropriate caloric intake and exercise is a key component of prevention. In patients with intellectual disability, involvement of caregivers in exercise and appropriate caloric intake is mandatory.		

Complications	Timeframe	Likelihood
nephrolithiasis	**long term**	**medium**
Hyperphosphatemia is commonly seen in patients with PHP. Hyperphosphatemia results in the formation of calcium phosphate kidney stones. Nephrolithiasis can be prevented by monitoring urine calcium levels. Dose adjustments are necessary in patients with hypercalciuria to avoid nephrolithiasis. Patients should also be counseled on adequate fluid intake, because concentration of the urine increases the risk of stone formation. Normalization of phosphate levels also helps prevent this complication and can be achieved using phosphate-binding calcium supplements.		
infertility	**long term**	**low**
Signaling of gonadotropins occurs through G-proteins, and a loss of this second messenger results in maturational delay, oligomenorrhea, and infertility. Gonadotropin resistance is a feature of type Ia and Ic PHP. Patients with type Ia PHP who develop pubertal delay and oligomenorrhea should be screened for low sex steroid levels. Treatment with hormone replacement is usually required.		
osteomas	**long term**	**low**
Some patients with Albright hereditary osteodystrophy develop extraskeletal osteomas, which may be symptomatic. Surgical evaluation may be required for symptom amelioration.[51]		
spinal cord compression	**long term**	**low**
Reported, due to diffuse ossification of the posterior longitudinal ligament and ligamentum flavum.[52] [53] Surgical decompression may be required to ameliorate the symptoms.		
fetal limb reduction defects	**long term**	**low**
If a patient with PHP becomes pregnant, there is a risk of limb abnormalities developing in the fetus. The process of normal growth plate formation is regulated by the intricate interplay of a transcription factor, Indian hedgehog, and the PTH-related protein (PTHrP).[54] PTHrP acts predominantly through the G-protein/cyclic adenosine monophosphate pathway in chondrocytes, and is the major regulator of calcium and phosphorus metabolism during pregnancy. The loss of G-protein signaling in the mother leads to PTHrP resistance, with early closure of the growth plate, and limb reduction defects. Few case reports have been published regarding surveillance and treatment of PHP during pregnancy and lactation, though one retrospective observational study highly recommended intense biochemical, clinical, and pharmacologic monitoring during pregnancy and breastfeeding.[55] [56] More studies are needed to find out how best to prevent this complication.		

FOLLOW UP

Prognosis

Little is known of the long-term outcomes of pseudohypoparathyroidism (PHP) because the condition is rare, and published data are confined to case series and case reports. The underlying cause of PHP is incurable. However, some patients have resolution of hypocalcemia with time as calcium homeostasis adapts to parathyroid hormone (PTH) resistance. Those who do not adapt to PTH resistance require lifelong calcium supplementation. Patients with associated hypothyroidism require long-term levothyroxine therapy. Rarely, other endocrinopathies can occur in type Ia or Ic PHP. Gonadotropin resistance can cause delayed puberty or infertility. Growth hormone-releasing hormone (GHRH) resistance can produce growth hormone deficiency. It is important to remain alert for symptoms and signs of these endocrinopathies, and to initiate testing of the gonadotropin or GHRH axes if required.

Diagnostic guidelines

International

Primer on the metabolic bone diseases and disorders of mineral metabolism (http://www.asbmr.org/Publications/Primer/Default.aspx) [4]

Published by: American Society for Bone and Mineral Research **Last published:** 2018

Recommendations for diagnosis and treatment of pseudohypoparathyroidism and related disorders: an updated practical tool for physicians and patients (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8140671) [2]

Published by: European Cooperation in Science and Technology; European Network for Human Congenital Imprinting Disorders; European Reference Network on Rare Endocrine Conditions; European Reference Network on Rare Bone Disorders; European Calcified Tissue Society; Asian Pacific Paediatric Endocrine Society; European Society of Human Genetics; Pediatric Endocrine Society; European Society of Endocrinology; European Society for Paediatric Endocrinology **Last published:** 2020

Diagnosis and management of pseudohypoparathyroidism and related disorders: first international consensus statement (https://www.nature.com/articles/s41574-018-0042-0) [1]

Published by: European Cooperation in Science and Technology; European Network for Human Congenital Imprinting Disorders; European Reference Network on Rare Endocrine Conditions; European Reference Network on Rare Bone Disorders; European Calcified Tissue Society; Asian Pacific Paediatric Endocrine Society; European Society of Human Genetics; Pediatric Endocrine Society; European Society of Endocrinology; European Society for Paediatric Endocrinology **Last published:** 2018

Treatment guidelines

International

Primer on the metabolic bone diseases and disorders of mineral metabolism (http://www.asbmr.org/Publications/Primer/Default.aspx) [4]

Published by: American Society for Bone and Mineral Research **Last published:** 2018

Recommendations for diagnosis and treatment of pseudohypoparathyroidism and related disorders: an updated practical tool for physicians and patients (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8140671) [2]

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Online resources

1. NIH Osteoporosis and Related Bone Diseases National Resource Center (http://www.niams.nih.gov/Health_Info/Bone) *(external link)*

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Images

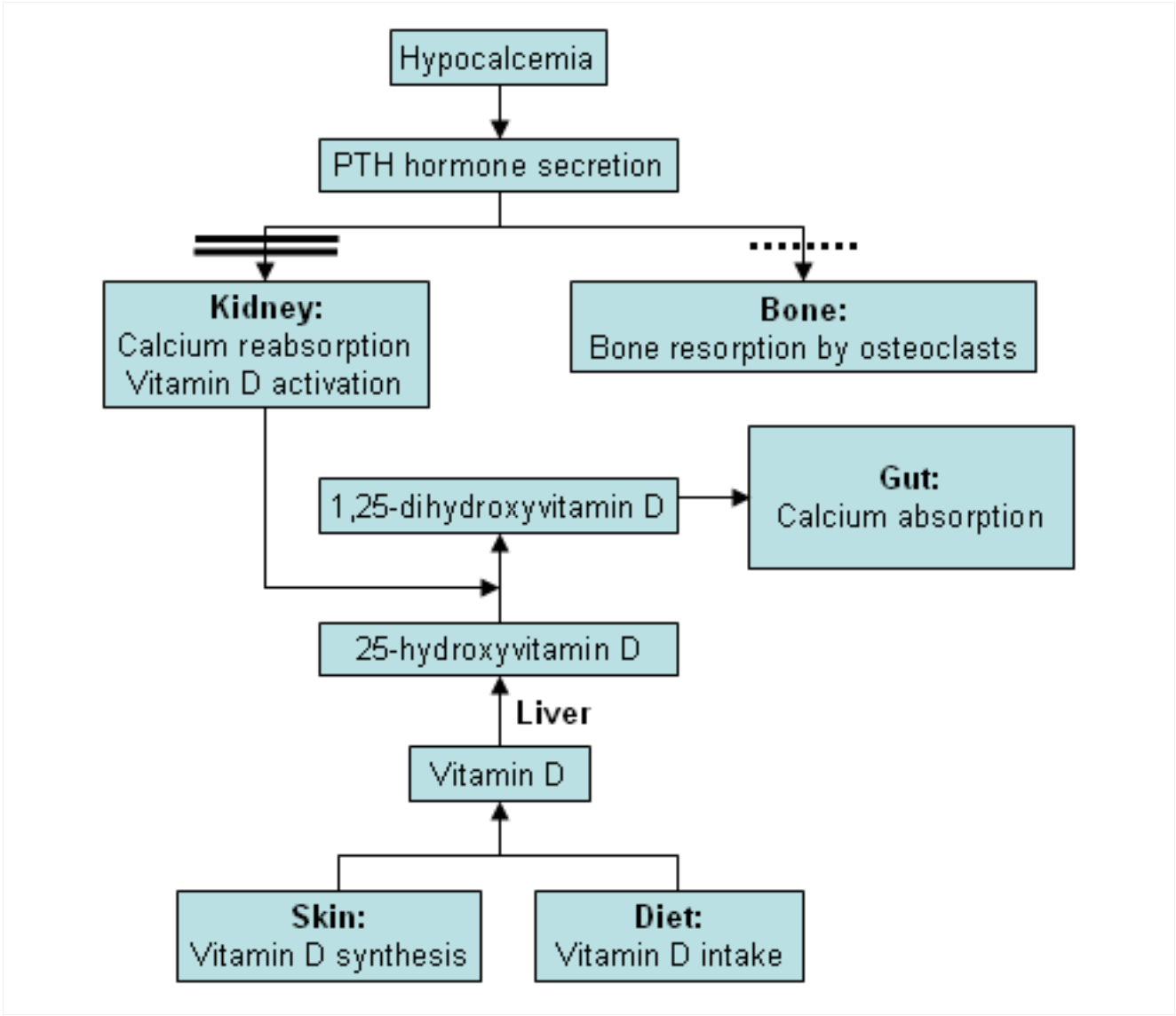

Figure 1: Overview of regulation of serum calcium. The double lines and dashed line indicate the defects in PTH signaling seen in PHP. The defect in the kidney response is more pronounced

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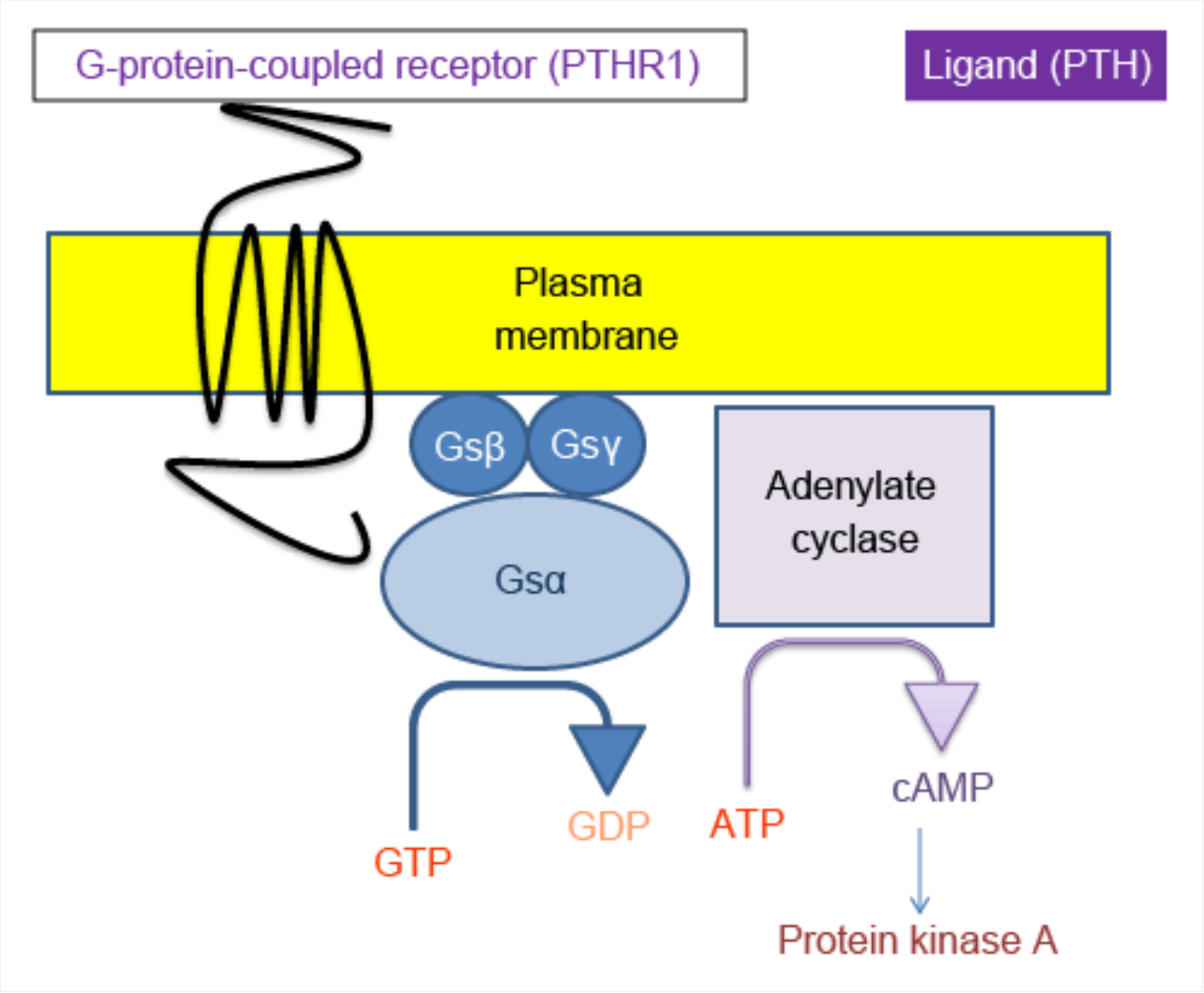

Figure 2: The signaling cascade of parathyroid hormone

From the collection of Kent Wehmeier, University of Florida Jacksonville

Ask the patient to relax his facial nerves. Next, stand directly in front of him and tap the facial nerve either just anterior to the earlobe or below the zygomatic arch and the corner of the mouth. A positive response varies from twitching of the lip at the corner of the mouth to spasm of all facial muscles, depending on the severity of hypocalcemia.

Figure 3: Eliciting Chvostek sign

Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

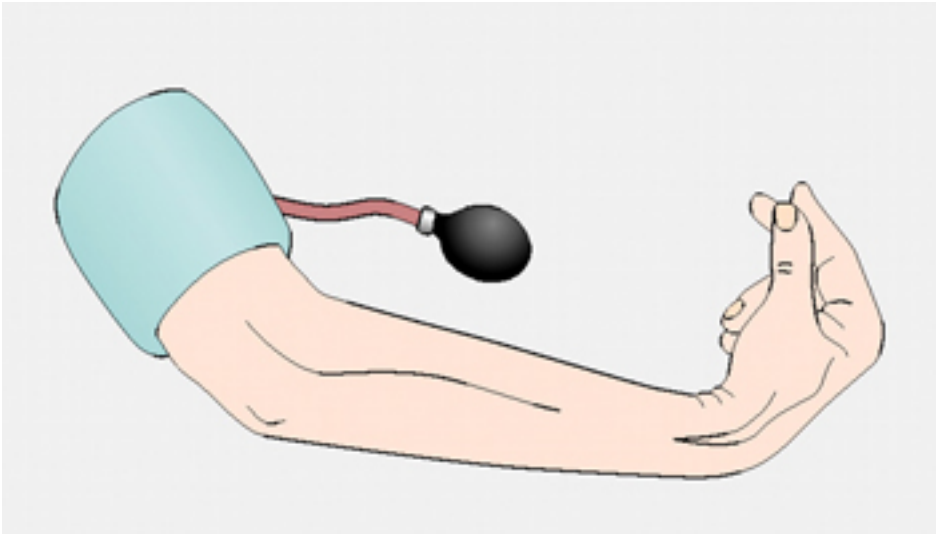

Figure 4: Eliciting Trousseau sign

Cooper MS, Gittoes NJL. BMJ. 2008 Jun 7;336(7656):1298-302

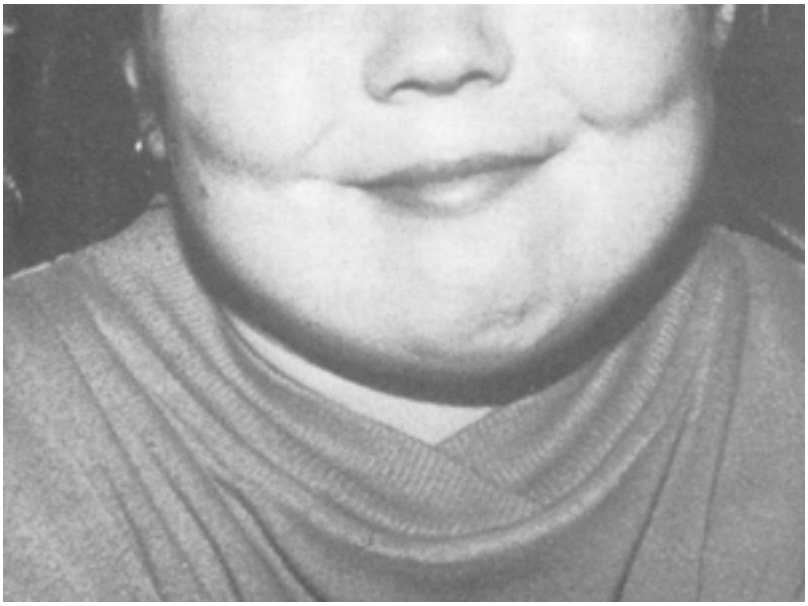

Figure 5: Child with Albright hereditary osteodystrophy showing a round face and a short nose with a flat nasal bridge

Wilson LC, Trembath RC. J Med Genet. 1994 Oct;31(10):779-84

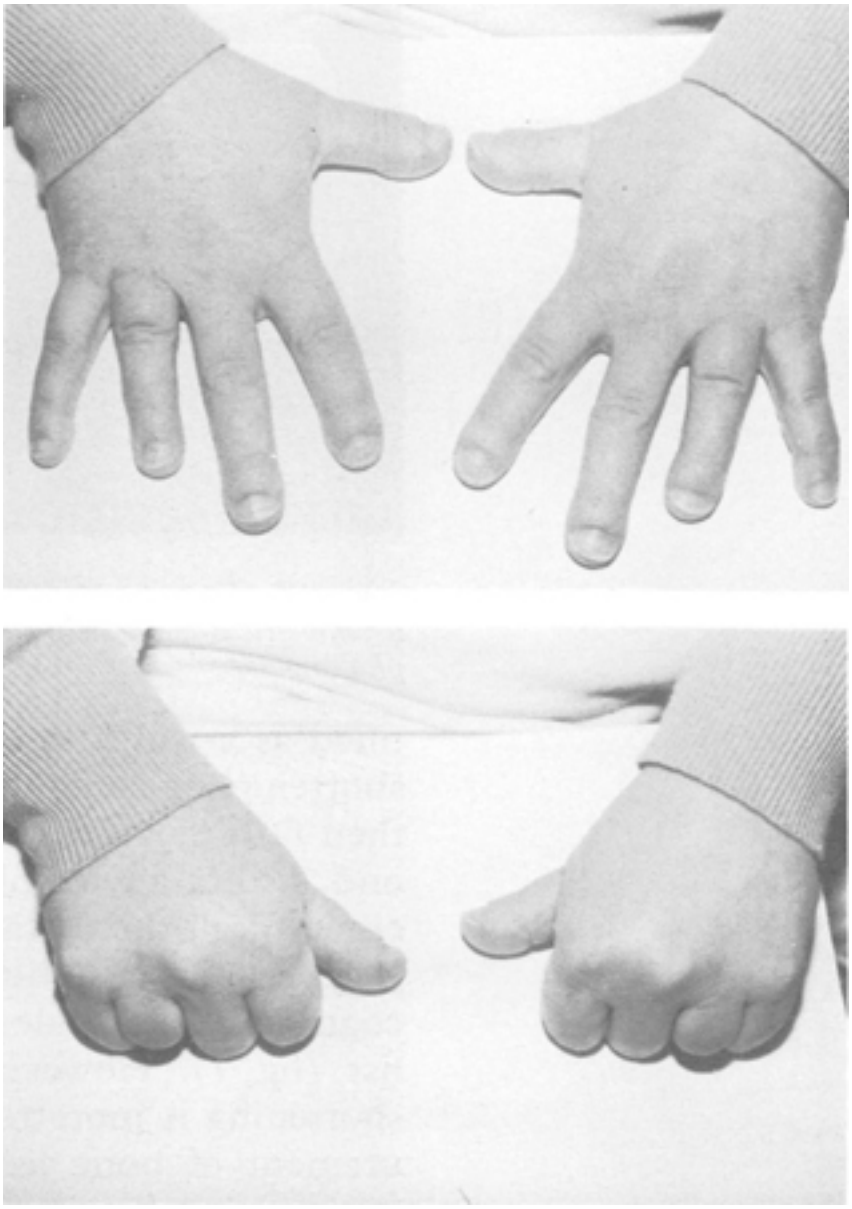

Figure 6: Hands of an adult with Albright hereditary osteodystrophy showing shortening of the IV metacarpal and distal phalanges, and knuckle dimples in the clenched fists

Wilson LC, Trembath RC. J Med Genet. 1994 Oct;31(10):779-84

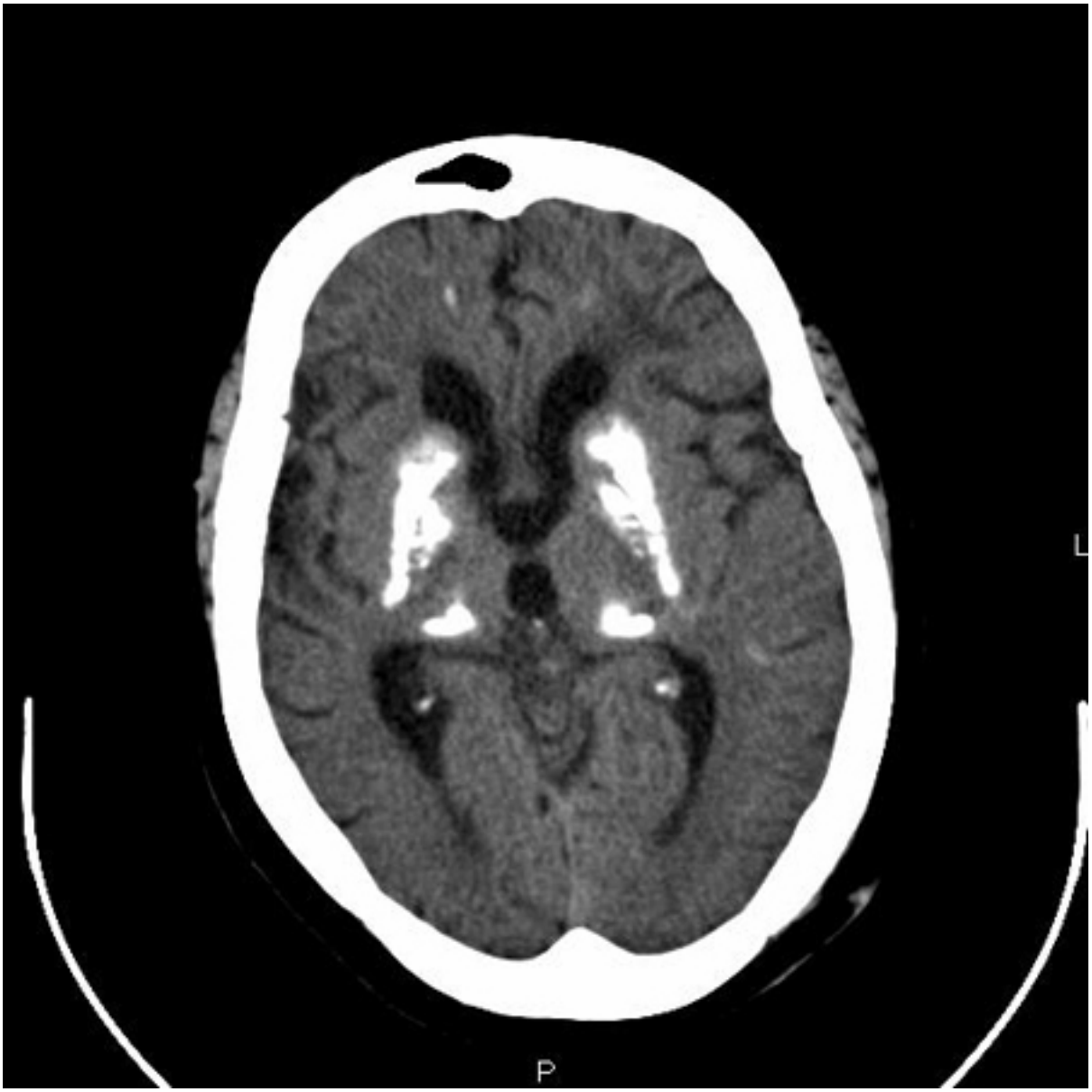

Figure 7: CT findings of severe basal ganglia calcification in a patient with pseudohypoparathyroidism

From the collection of Kent Wehmeier, University of Florida Jacksonville

	Type Ia	Type Ib	Type Ic	Type II	Pseudo-PHP
AHO	yes	no	yes	no	yes
Calcium level	low	low	low	low	normal
PTH level	high	high	high	high	normal
Response to exogenous PTH	↓urine cAMP ↓urine phosphorus	↓urine cAMP ↓urine phosphorus	↓urine cAMP ↓urine phosphorus	normal urine cAMP ↓urine phosphorus	normalurine cAMP normalurine phosphorus
GNAS gene mutations	maternal inactivating mutations	imprinting dysregulation	few inactivating mutations reported	none	paternal inactivating mutations
Hormone resistance	multiple: PTH, TSH, Gn, GHRH	PTH, TSH	multiple: PTH, TSH, Gn	PTH only	none

AHO: Albright hereditary osteodystrophy; Pseudo-PHP: pseudopseudohypoparathyroidism; cAMP: cyclic adenosine monophosphate; PTH: parathyroid hormone; TSH: thyroid stimulating hormone; Gn: gonadotropins; GHRH: growth hormone releasing hormone

Figure 8: Subtypes of pseudohypoparathyroidism

Created by Dr Emad Naem

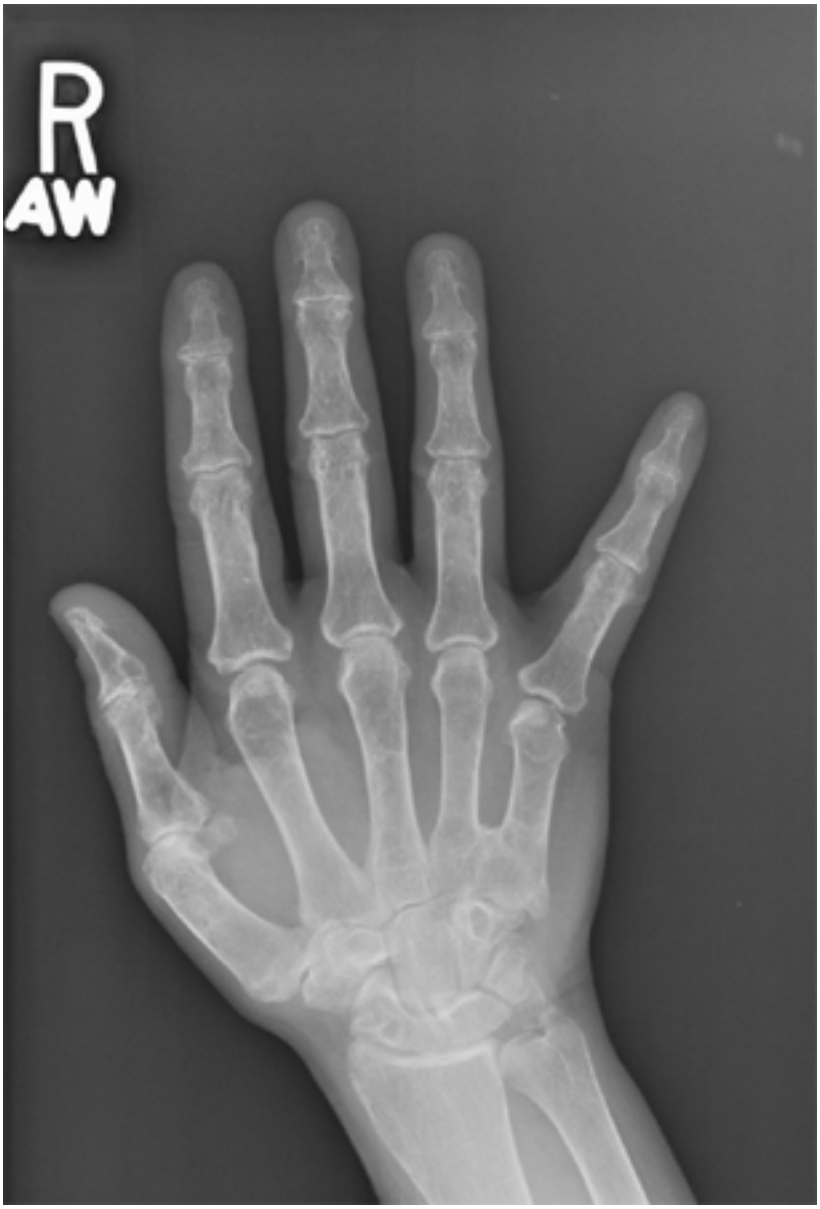

Figure 9: Hand radiograph suggestive of shortened IV and V metacarpals

From the collection of Kent Wehmeier, University of Florida Jacksonville

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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