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ABSTRACT

The principal function of the parathyroid hormone (PTH) is maintenance of calcium plasmatic levels, withdrawing the calcium from bone tissue, reabsorbing it from the glomerular filtrate, and indirectly increasing its intestinal absorption by stimulating active vitamin D (calcitriol) production. Additionally, the PTH prompts an increase in urinary excretion of phosphorus and bicarbonate, seeking a larger quantity of free calcium available in circulation. Two mechanisms may alter its function, limiting its control on calcium: insufficient PTH production by the parathyroids (hypoparathyroidism), or a resistance against its action in target tissues (pseudohypoparathyroidism). In both cases, there are significantly reduced levels of plasmatic calcium associated with hyperphosphatemia. Clinical cases are characterized by nervous hyperexcitability, with paresthesia, cramps, tetany, hyperreflexia, convulsions, and tetanic crisis. Abnormalities such as cataracts and basal ganglia calcification are also typical of these diseases. Treatment consists of oral calcium supplementation associated with increased doses of vitamin D derivatives. (**Arq Bras Endocrinol Metab 2006;50/4:664-673**)

Keywords: Hypoparathyroidism; PTH; Hypocalcemia; Pseudohypoparathyroidism; PTH resistance; Albright hereditary osteodystrophy

RESUMO

Hipoparatiroidismo e Pseudohipoparatiroidismo.

A principal função do paratormônio (PTH) é a manutenção dos níveis plasmáticos de cálcio, retirando-o do tecido ósseo, reabsorvendo-o do filtrado glomerular e, indiretamente, aumentando sua absorção intestinal através do estímulo para a produção de vitamina D ativa (calcitriol). Além disso, o PTH promove um aumento na excreção urinária de fósforo e bicarbonato, objetivando uma maior quantidade de cálcio livre disponível na circulação. Dois mecanismos podem alterar sua função, limitando seu controle sobre o cálcio: produção insuficiente de PTH pelas paratiróides (hipoparatiroidismo), ou uma resistência à sua ação nos órgãos-alvo (pseudohipoparatiroidismo). Em ambos os casos, ocorre uma redução significativa dos níveis plasmáticos de cálcio em associação com hiperfosfatemia. Manifestações clínicas características são: hiperexcitabilidade nervosa, com parestesia, câimbras, tetania, hiperreflexia, convulsões e crise tetânica. Catarata e calcificação dos gânglios basais são anormalidades típicas dessas doenças. O tratamento consiste da suplementação oral de cálcio, associada com doses elevadas de derivados da vitamina D. (**Arq Bras Endocrinol Metab 2006;50/4:664-673**)

Descritores: Hipoparatiroidismo; PTH; Hipocalcemia; Pseudohipoparatiroidismo; Resistência a PTH; Osteodistrofia hereditária de Albright

HYPOCALCEMIA: CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

SERUM CALCIUM CONCENTRATION is kept within a narrow physiological range due to complex control mechanisms involving the parathyroid hormone (PTH), active vitamin D ($1.25(\text{OH})_2\text{D}$), and calcium sensor receptors, in addition to the concentrations of calcium and phosphate, which act in the renal, intestinal, and bone tissues in order to maintain calcium homeostasis. Hypocalcemia occurs when homeostatic mechanisms fail or when they are not fully compensated.

The normal range of total serum calcium is between 8.5 and 10.2 mg/dL (2.12 to 2.55 mmol/L). Symptoms of hypocalcemia occur when the level of ionized calcium is below 2.8 mg/dL (0.7 mmol/L), equivalent to 7.0 to 7.5 mg/dl (1.75 to 1.87 mmol/l) of total calcium (1,2). The severity of symptoms and clinical signs of hypocalcemia correlates with the magnitude and speed at which calcium declines, influenced by acid-base status and presence of hypomagnesemia and/or sympathetic hyperactivity.

Acute hypocalcemia

In acute and/or severe symptomatic hypocalcemia there is a predominance of neuromuscular, neuropsychiatric, and cardiovascular abnormalities. There is an increase in neuromuscular excitability, latent or evident, with sensory and motor disruption. Perioral or extremity paresthesia, cramps, myalgia, and muscular weakness are mild to moderate symptoms. Smooth muscle spasms may cause biliary and intestinal cramps, dysphagia, bronchospasms, laryngeal stridor, premature birth, and detrusor muscle dysfunction. Severe hypocalcemia manifests as spontaneous tetany, which may appear in the form of carpopedal spasms and, more rarely, laryngospasms. Neuropsychiatric manifestations include irritability, anxiety, psychosis, hallucinations, dementia, depression, mental confusion, and extrapyramidal abnormalities. Increased intracranial pressure, papilledema, and convulsions can also be present, and must be differentiated from severe tetany muscular spasms (3-5).

Typical clinical signs of neuromuscular irritability associated with latent tetany include hyperreflexia and Chvostek's and Trousseau's signs, respectively. Chvostek's sign is obtained by the percussion of the facial nerve approximately 2 cm anterior to the ear lobe, causing contraction of the ipsilateral facial muscles. It has low specificity and sensibility; 25% of healthy individuals present a positive sign, while 29% of hypocalcemic individuals present a negative sign. Trousseau's sign is more reliable; 94% of hypocalcemic

individuals and only 1 to 4% of healthy individuals present a positive sign, which is obtained by pressurizing a sphygmomanometer approximately 20–30 mmHg above systolic pressure for 3 minutes. It is characterized by carpal spasms, with adduction of the thumb, followed by flexion of the metacarpophalangeal joint, extension of the interphalangeal joints, and flexion of the wrist, creating the classic "obstetrician's hand" pose, in addition to causing paresthesia, muscular tension, and local cramps (6).

Severe hypocalcemia may result in bradycardia or ventricular arrhythmias, cardiovascular collapse, and hypotension that is non-responsive to fluids and vasopressors. A decrease in myocardial contractility occurs, as well as a typical electrocardiographic abnormality, which is the rate-corrected QT interval (QT_c) prolongation.

Chronic hypocalcemia

Patients with chronic hypocalcemia may or may not have symptoms of discreet neuromuscular irritation, even with markedly low calcium levels. Asymptomatic cases may be detected by chance, by the dosage of calcium in routine exams, during periods of greater calcium demand (i.e.: gestation, lactation, menstrual cycle and states of alkalosis), or during the use of hypocalcemic drugs (i.e.: bisphosphonates). Ectodermic abnormalities from dry skin to dermatitis and even alopecia are common. Dental abnormalities suggest the time of hypocalcemic onset. In infancy, it may lead to dental or enamel hypoplasia, the delay or absence of permanent tooth eruption, an increase in cavity occurrence, the shortening of molar roots, and, in some cases, the loss of all teeth (7).

Significant cognitive deficits, neuropsychiatric abnormalities, and extrapyramidal symptoms that resemble Parkinson's disease or chorea are associated with the calcification of basal ganglia, which occurs in all forms of chronic hypocalcemia and may be detected with greater sensibility using computerized tomography (8).

Other findings of chronic hypocalcemia include sub-capsular cataracts, an increase in bone mineral density (BMD), and greater susceptibility to dystonic reactions induced by phenothiazines (4).

Differential diagnosis of hypocalcemia

Ionized or free calcium dosages are quicker, which will make them more useful during urgent situations. Hypocalcemia must be confirmed by the measurement of total plasmatic calcium, which should always be corrected in hypoalbuminemia cases (plasmatic albumin < 4 mg/dL) according to the following formula:

Corrected Serum Ca = Total Serum Ca mg/dL (0.8 x [(4 - albumin mg/dL)]).

Differential diagnosis of hypocalcemia will depend largely upon PTH and phosphorus levels, evaluated along with other clinical and laboratory data (table 1). Cases presenting hypophosphatemia should include differential diagnosis of vitamin D, while cases associated with hyperphosphatemia are determined according to PTH levels.

HYPOPARATHYROIDISM

Hypoparathyroidism is an abnormality caused by a parathyroid hormone (PTH) secretion deficiency, and encompasses heterogeneous conditions (table 1), which makes etiological differentiation crucial to the detection of abnormalities associated with some of these diseases beforehand, thereby preventing complications (4). Signs and symptoms are caused by hypocalcemia. Laboratory measurements present hypocalcemia, hyperphosphatemia, and inappropriately low or undetectable PTH. Generally, levels of 1.25(OH)₂D are low and the alkaline phosphatase is normal. In the majority of cases, hypoparathyroidism is sporadic, but there are familial cases in which transmission may be autosomic recessive, dominant, or X-linked.

The most common cause of hypoparathyroidism is after thyroid surgery. Incidence of perma-

nent hypoparathyroidism varies and depends on the root disease, extent of surgery, and surgeon's experience. Symptoms generally begin 1 or 2 days after the procedure, and in approximately 50% of the cases this abnormality is transient and caused by edema or glandular hemorrhage. After the removal of 1 or more parathyroids for the treatment of primary hyperparathyroidism, hypocalcemia indicate 2 etiologies: Hungry Bone Syndrome or hypoparathyroidism. Differentiation is made via measurements of phosphorus, which will be low in Hungry Bone Syndrome and high in hypoparathyroidism. Hypoparathyroidism may be a rare complication after radioactive iodine treatment or external radiotherapy on the cervical region (9,10).

Autoimmunity may also be another cause of hypoparathyroidism, which may be isolated or associated with other autoimmune diseases (11). Antibodies against parathyroids were detected in more than 30% of patients with isolated hypoparathyroidism and more than 40% of patients with hypoparathyroidism associated with other endocrine deficiencies. Antibodies against the calcium sensor-receptor (CASR) have been found in more than 50% of patients with polyglandular autoimmune syndrome type I or hypoparathyroidism associated with autoimmune hypothyroidism. The polyglandular autoimmune syndrome type I is characterized by the triad: hypoparathyroidism (which is the most frequent endocrinopathy), mucocutaneous candidiasis, and adrenal insufficiency. It is caused by a mutation in the autoimmune regulator gene (AIRE),

Table 1. Causes of hypocalcemia.

Low PTH levels (hypoparathyroidism)	High PTH levels (secondary hyperparathyroidism)
<i>Parathyroid Destruction</i>	<i>PTH resistance</i>
Surgery	Pseudohypoparathyroidism
Auto-immune (isolated or polyglandular)	Hypomagnesemia
Cervical irradiation	<i>Vitamin D deficiency</i>
Infiltration by metastasis or systemic diseases (Sarcoidosis, amyloidosis, hemochromatosis, Wilson's disease, thalassemia)	Nutritional
<i>Reduced parathyroid function</i>	Lack of sunlight
Hypomagnesemia	Malabsorption
PTH gene defects	Vitamin D dependent rickets
Calcium sensing receptor mutations	type I (lack of activity of 1 α -hydroxylase)
<i>Parathyroid agenesis</i>	type II (Vitamin D receptor resistance)
DiGeorge Syndrome	Chronic renal disease
Isolated x-linked hypoparathyroidism	<i>Drugs</i>
Kenny-Caffey syndrome	Bisphosphonates, cisplatin, ketoconazole, gallium nitrate, anticonvulsants
Mitochondrial neuropathies	<i>Hyperphosphatemia</i>
	Renal insufficiency
	Massive tumor lysis
	Acute rhabdomyolysis
	<i>Acute pancreatitis</i>
	<i>Hungry bone</i>
	<i>Toxic shock syndrome</i>
	<i>Acute severe illness</i>
	<i>Calcium chelators (citrate blood transfusions, phosphate)</i>

located in locus 21q22.3, which produces a protein that functions as a transcription regulator. This syndrome may be sporadic or familial, with autosomic recessive transmission. Clinical signs begin to appear in patients approximately 5 years after birth with the emergence of candidiasis, followed by hypoparathyroidism before the age of 10, and later adrenal insufficiency, found in 100%, 79%, and 72% of the cases, respectively (11,12). Hypogonadism, hypothyroidism, insulin-dependent mellitus diabetes, alopecia, vitiligo, keratoconjunctivitis, intestinal malabsorption syndrome, chronic hepatitis, and pernicious anemia may also be present.

Maternal hyperparathyroidism, which inhibits PTH secretion by newborns' parathyroids, is another cause of hypoparathyroidism. Hypocalcemia generally develops in the third week of life and is self-contained (10). Variations in magnesium levels may also cause hypoparathyroidism. Hypermagnesemia stimulates the CASR and inhibits PTH secretion. In such circumstances, the clinical case of neuromuscular hyperexcitability is usually more discreet. Hypomagnesemia, commonly seen in chronic alcoholism and burn victims, may also cause hypocalcemia because it promotes the diminution of PTH secretion levels in addition to causing renal and bone resistance to PTH action (13).

DiGeorge Syndrome is characterized by thymus and parathyroid dysgenesis, cardiac malformation, and facial dysmorphogenesis. There is a defect in the formation of the third and fourth bronchial arches, owed to the deletions of locus 22q11.2, but the gene responsible for the syndrome has yet to be identified. Some patients with phenotype similar to DiGeorge Syndrome present deletions in other chromosomes (10p13 and 10p14) (14). The agenesis or dysgenesis of isolated parathyroids have X-linked or autosomic recessive transmission. Cases with X-linked transmission are related to a mutation in locus Xq26-27, which likely plays a role in the embryological development of parathyroids (10).

Another genetic cause is HDR Syndrome, characterized by hypoparathyroidism, neuro-sensorial deafness, and renal dysplasia. HDR is related to haploinsufficiency or function loss of gene GATA3 (GATA binding protein 3), located in chromosome 10p14-10, which belongs to the family of transcription factors involved in embryological development (15).

Other complex syndromes associated with hypoparathyroidism are: Sanjat-Sakati syndrome (hypoparathyroidism, mental retardation, stunted growth, dysmorphism, and seizures, related to a muta-

tion in the chromosome region 1q43-44); Kenny-Caffey Syndrome (stunted growth, facial-cranial abnormalities, long bone cortical thickening, with medullary stenosis and basal ganglia calcification); mitochondrial myopathies, such as Kearns-Sayre Syndrome (encephalomyopathy, ophthalmoplegia, retinal pigment dystrophy and cardiomyopathy) and Pearson's marrow-pancreas syndrome (neutropenia, sideroblastic anemia, vacuolization of the bone marrow cells, and exocrine pancreas dysfunction) (10).

Patients classified as having idiopathic hypoparathyroidism must be carefully evaluated in order to exclude genetic syndromes. Genetic studies have linked these cases to mutations in the CASR and PTH genes. The CASR gene, bound to the G protein and comprising 1078 amino acid residues, is located in chromosome 3q and codifies a cell surface receptor belonging to family C of the seven transmembrane receptor (7TM) superfamily (16,17). Predominantly expressed in the parathyroids and kidneys, this receptor regulates PTH secretion and the tubular excretion of calcium in response to fluctuations in calcium serum levels. When extra-cellular calcium concentrations increase, the CASR activates the G protein pathway, stimulating the activity of phospholipases C, leading to the accumulation of inositol 1,4,5 triphosphate (IP3) and the liberation of calcium from intra-cellular storage. The increase of intracellular calcium results in the activation of protein kinase C, which in turn activates the MAPK's pathway, reducing the PTH gene transcription (15-17). The CASR is found in tissues unrelated to calcium homeostasis, such as the mammal gland, keratinocytes, central nervous system, pancreas, and epithelial cells, although its function has yet to be defined (16). Mutations that lead to function loss in this gene are related to familial benign hypocalciuric hypercalcemia and severe neonatal primary hyperparathyroidism (15,17). Activating mutations, on the other hand, cause a decrease of the calcium set point, promote the suppression of PTH, and induce hypercalciuria, which may aggravate the hypocalcemia. Mutations are generally located in the aminoterminal domain of the extra-cellular and transmembrane portions of the CASR. Exons 3, 4 and 7 are considered hotspots for activating mutations in this gene. Exons 3 and 4 involve the extra-cellular domain, an essential portion of the receptor for glycosylation, cell surface expression, dimerization, and binding of the ligand. Mutations in exon 7 involve domains that participate in the activation of G proteins associated with the receptor (18). Lienhardt and colleagues showed a high frequency of CASR mutations (42%) in patients with

isolated hypoparathyroidism, placing added importance on the screening of this gene, especially in hypocalcemic patients showing normal urinary calcium excretion (relative hypercalciuria). Since there is an excellent correlation between the presence of mutation in the CASR and hypocalcemia, the measurement of the serum calcium may be used as a sufficiently sensitive screening in the affected families with this abnormality (18). Patients are generally asymptomatic, the serum PTH is normal or low, and they receive the hypoparathyroidism diagnosis (15). It is important to distinguish these patients from those with hypoparathyroidism, because their treatment with calcium and vitamin D may lead to hypercalciuria, nephrocalcinosis, and loss of renal function (10).

Mutations of the PTH gene, located in locus 11p15, are uncommon causes of hypoparathyroidism, and they can present autosomic recessive or dominant modes of inheritance. They result in defective PTH molecule synthesis and undetectable PTH levels. Another gene related to hypoparathyroidism is GCMB (a human gene homologous to the *Drosophila* glial cell missing gene b), located in chromosome 6p24.2, expressed exclusively in the parathyroids, and which codifies an important transcription factor for the development of these glands (10). The *Gcm2* (glial cells missing 2) is the murine gene homologous for GCMB. Homozygote knockout rats (-/-) for the *Gcm2* do not present parathyroids and develop hypocalcemia and hyperphosphatemia. PTH levels are normal or low, but insufficient to control hypocalcemia. In these rats there may also be PTH production by parathyroid cells located in the thymus capsule, explaining the diminished, but detectable, PTH levels. In humans it is unknown if there is intrathymic PTH production or if this small PTH production is due to the gene's residual activity (15,19).

PSEUDOHYPOPARATHYROIDISM

The term pseudo-hypoparathyroidism describes a group of abnormalities characterized by clinical and laboratorial hypoparathyroidism findings (hypocalcemia, hyperphosphatemia), but with high plasmatic levels of PTH due to a target tissue resistance, if chronic renal failure or magnesium deficiency were excluded (20).

Historical

In 1942, Fuller Albright and cols. described 3 patients with clinical and laboratorial hypocalcemia findings in which the administration of parathyroid tissue extracts

did not promote an increase in serum calcium or phosphaturia (21). These individuals presented development abnormalities: rounded face, short stature, obesity, brachydactyly, short and low-set nasal bridge, strabismus, and ectopic calcifications; which were designated Albright's Hereditary Osteodystrophy (AHO). Due to biochemical similarities with hypoparathyroidism, but associated with high levels of PTH was called pseudo-hypoparathyroidism (PHP). In 1966, Tashjian et al. (22) demonstrated an increase in serum PTH concentrations in these patients and, in 1969, Chase et al. (23) presented that there was no urinary AMPc generation in patients with PHP and the pathogenesis of this abnormality should be related to a renal defect in the generation of urinary AMPc by the PTH receptor.

PTH receptor type I

PTH receptor type I is expressed in the kidney and bone as a glycoprotein of approximately 75 kDa that connects to both PTH and PTH-related protein (PTHrP). This receptor, attached to regulatory heterotrimeric protein G (α , β , γ), presents a single polypeptide chain with seven transmembrane domains, 3 extracellular loops, and 3 or 4 intracellular loops (20).

Hormone binding leads to the activation of protein G_s , with disassociation of subunit α . This, when activated, disconnects itself from the receptor and functions as a primary modulator of the adenyl cyclase, promoting the intracellular formation of cyclic AMP (AMPc), which rapidly activates the protein kinase A (PKA) (21-25). The intrinsic GTPase activity of subunit α permits the linking of $\beta\gamma$ dimer for a new activation cycle.

Patients with AHO present inactivating mutations in the *GNAS1* gene, which codifies the subunit α of protein G_s , mapped in chromosome 20q13.2-20q13.3. The *GNAS1* gene is codified by 13 exons, in addition to 3 initial exons that correspond to different promoters, allowing, by alternative splicing, the formation of 4 different isoforms. Exons 2-13 are common to all transcripts. Mutations were described in all exons, except in 3, which despite suffering splicing out still produced a functional protein (26).

Recent studies confirm that the *GNAS1* gene presents the imprinting phenomenon, which explains the variations in phenotype depending upon the maternal or paternal mutation's origin (24,27,28). Three promoters present opposing models of allele-specific methylation and monoallelic transcription. The promoter closest to the 5' extremity codifies region NESP55 (neuroendocrine secretory protein

55), which is expressed exclusively by the maternal allele, while exons $XL_{\alpha S}$ (extra large as like protein) and 1A (1 alternative) are expressed by the paternal allele (figure 1). Despite simultaneous imprinting (paternal and maternal), expression of $G_s\alpha$ appears to be biallelic in the majority of examined human tissues, but expressed maternally in only some tissues such as the proximal renal tubules (25).

Pathogenesis and classification

The characterization of the molecular bases of pseudo-hypoparathyroidism began with the observation that the AMPc is the mediator of various PTH actions in the kidney and bone fiber.

PTH infusion remains the most consistent test for the distinction of the diverse variants of this syndrome. Based in the abnormalities of the various components of the transduction of the cell membrane signal, the pseudo-hypoparathyroidism may be divided in distinct forms.

Pseudo-hypoparathyroidism type 1a (PHP1a)

Presents AHO phenotype. There is a reduction in activity of the stimulatory protein G (G_s), limiting AMPc synthesis. In this situation, patients are not only resistant to PTH, but to other *peptide hormones* like TSH, gonadotrophins, and glucagon. Transmission is autosomic dominant (29). Hypocalcaemia and hyperphosphatemia are not typically present until five years of age, but PTH elevations may be documented much earlier and sometimes are associated with light hypercalcemia. Primary hypoparathyroidism frequently precedes the development of functional hypoparathyroidism and may be detected during neonatal screening. Gonadal dysfunction (hypogonadism or delayed puberty) is very frequent, especially in women (30). There are accounts of resistance to GHRH and prolactin deficiency in PHP1a cases (25,31,32). There is considerable variability in relation to tissue responsive-

ness to G_s protein deficiency, which may also be explained by the differences in the quantity of AMPc necessary in order to activate the kinase proteins and generate physiological responses in each tissue. The absence of imprinting in other target tissues would be another explication for patients with PHP1a who do not develop resistance to other hormones that stimulate the $G_s\alpha$ protein and paths linked to the AMPc (for example: ACTH and vasopressin) (25,26).

Pseudo-hypoparathyroidism type 1b (PHP1b)

Presents normal appearance, normal G_s activity, and isolated resistance to PTH. Molecular studies do not show an intrinsic defect in the PTH receptor, and present normal G_s function in the erythrocytes (25). The majority of cases appear to be sporadic, but some familial cases were described as having autosomic dominant transmission (29,33). As in PHP1a, a defective nephrogenic answer to AMPc occurs in relation to PTH. However, these individuals present elevated PTH concentrations and frequently manifest skeletal abnormalities similar to those that occur in patients with hyperparathyroidism (30). Fibroblast studies show small accumulation of AMPc in response to PTH in some cases associated with lower quantities of the PTH type I Receptor *RNA*. A molecular defect was mapped in a small region of chromosome 20q13.3 (exon 1A) next to the *GNAS1* gene. Exon 1A is important to maintain the tissue-specific imprinting of $G_s\alpha$ and is normally methylated in the maternal allele and not methylated in the paternal allele (25). One of the proposed mechanisms to explain PHP1b cases was suggested by Weinstein and cols. (figure 2). Exon 1A contains a cis-acting, negative regulatory element (silencer) that is both methylation-sensitive and tissue-specific (25,26). A tissue-specific trans-acting repressor (R) binds to the silencer and suppresses G_s expression on the paternal allele, but is unable to bind the maternal allele due to methylation, allowing $G_s\alpha$ to be expressed from the maternal allele. In the majority of tissues, exon 1A is methylated but the repressor is not expressed, and as a result the $G_s\alpha$ is expressed biallelically. In PHP1b, the methylation of this exon is absent in the maternal allele, allowing the repressor to link to both alleles and suppress the $G_s\alpha$ expression in the renal proximal tubules, raising the $G_s\alpha$ deficiency and PTH resistance (26,29,34), which normally only express the maternal allele. These individuals do not present AHO, because the defective imprinting does not have an effect in the $G_s\alpha$ expression of the majority of the tissues where it is expressed biallelically.

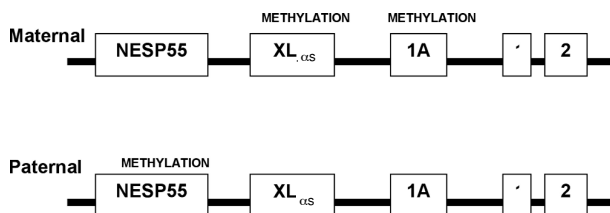


Figure 1. General organization and imprinting patterns of the *GNAS1* gene. Promoter NESP55 is only expressed by the maternal allele, while promoters $XL_{\alpha S}$ and 1A are expressed by the paternal allele.

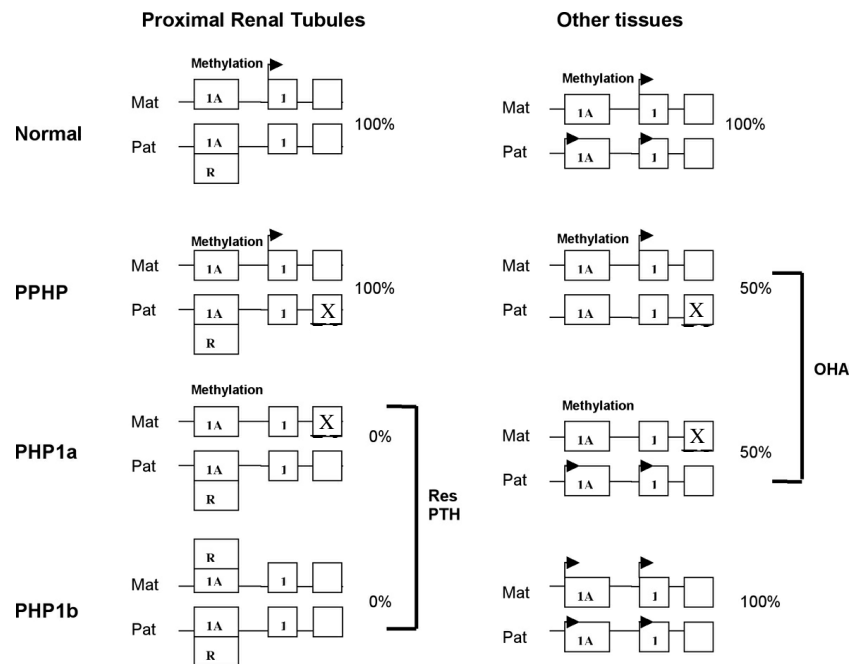


Figure 2. Mechanisms that explain the molecular pathogenesis of PTH resistance (res PTH) and Albright's Hereditary Osteodystrophy (AHO) by inactivation and imprinting of the GNAS1 gene. Exon 1A is only methylated in the maternal allele and is transcriptionally active in the paternal allele in all tissues. In the majority of tissues, exon 1A does not affect G_sα expression, which is biallelically expressed. In the proximal renal tubules, the non-methylated exon possibly suppresses G_sα expression in the paternal allele via a repressor (R), leading to a maternal-specific expression of G_sα. In PPHP and PHP1a, the inactive mutations in the paternal and maternal alleles, respectively, reduce the G_sα expression by 50%, and this haploinsufficiency produces the Albright phenotype. In the proximal tubules, mutations in the inactive paternal allele do not affect G_sα expression, while mutations in the active maternal allele produce PTH resistance. In PHP1b, the methylation defect in the maternal allele leads to a paternal-specific imprinting model of exon 1A in both alleles. When this happens, G_sα loses expression in the proximal tubules and there is a PTH resistance, but not affecting the expression in other tissues, which explains why these individuals do not possess Albright's phenotype (25).

Pseudo-hypoparathyroidism type 1c (PHP1c)

Presents Albright's phenotype and resistance to multiple hormones (PTH, TSH, gonadotrophins, and glucagon). G_s activity is normal, and so is G_i. Studies show reduced activity of the membrane's adenylyl cyclase catalytic subunit. It has yet to be clarified which molecular defect is responsible (29).

Pseudo-hypoparathyroidism type 2 (PHP2)

Some patients present normal phenotype, normal AMPc urinary excretion but absent phosphaturic response to PTH. It is probably associated with defects in stages posterior to AMPc formation, because G_s activity is normal. Its defect has yet to be identified and suggests that there is not any evidence of familial transmission and that it may be an acquired defect.

Pseudo-pseudohypoparathyroidism (PPHP)

The term was used by Albright to describe patients with the Albright phenotype, but without the labora-

torial findings (35). Some clinical syndromes, however, may present the same skeletal abnormalities as AHO without evidence of PTH resistance. PPHP carriers are often times relatives of PHP patients, and may present periods of hypocalcemia and normocalcemia. AHO patients who inherit G_sα mutations from their mothers also develop resistance to TSH, PTH, and gonadotrophins (PHP1a), while those who inherit it from their fathers develop only OHA (PPHP). This is owed to the fact that the G_sα gene is expressed primarily from the maternal allele in target-tissues for the respective hormones (renal proximal tubules, thyroid, and ovaries). Mutations in the active maternal allele lead to G_sα expression deficiency and hormonal resistance, while mutations of the paternal allele have little or no effect on genetic expression or hormonal signaling (26). The presence of a G_sα allele, however, is not sufficient in all tissues. Different phenotypes probably result from tissue-specific combinations of haploinsufficiency to paternal imprinting (maternal allele expres-

sion). The AHO phenotype results from deficient signaling in cells in which the $G_s\alpha$ gene is haploinsufficient but does not suffer imprinting (both alleles are expressed) (24). The diminution of signaling $G_s\alpha$ appears to promote osteoblastic differentiation, which may explain ectopic calcifications and premature closing of growth plates (25).

Defects outside the endocrine system

Although it is characterized by endocrine dysfunction, it may have abnormalities in organs whose functions are mediated by the AMPc path. Weinstock et al. (36) showed that patients with PHPIA have altered olfactory function if compared with PHPIB patients. The mental deficiency that occurs 50–75% of PHP-carrying individuals is also associated with G_s deficiency. Studies also show evidence of paternal imprinting in the brown and white adipose tissue, suggesting that obesity may be resultant of decreased $G_s\alpha$ expression in the adipose tissues, with diminution of the AMPc and lipolysis formation in response to β -adrenergic stimulus in the adipocyte (25,29).

TREATMENT OF HYPOCALCEMIA

Management of acute or severe symptomatic hypocalcemia must be made with intravenous calcium, with the goal of interrupting symptoms, preventing laryngeal spasm, and maintain total calcium levels above 7.0–7.5 mg/dL (ionized calcium greater than 0.7 mmol/L). Hyperphosphatemia, alkalosis, and hypomagnesemia, when present, must be corrected. At that moment, the 10 to 30 mL of 10% calcium gluconate should be made slowly (10 minutes – maximum of 30 mg/min) in bolus IV (93 to 279 mg of elementary calcium), and repeated as many times as necessary. After the grave acute symptoms have been suspended, a maintenance of calcium levels via continuous endovenous infusion of 0.5 to 1.5 mg/Kg/h (maximum of 100 mg/h) of elementary calcium for 4 to 6 hours should be made, using a solution with SG5% 900 ml + 100 ml of 10% gluconate (930 mg elementary calcium/liter). Serum calcium levels must be measured frequently in this period, and electrocardiographic monitoring must be done, especially in those patients using digitalics, due to growing levels or calcium predisposed to digitalis intoxication. Endovenous transition to the oral must be made as soon as possible (2,3,38).

Long-term treatment of patients with chronic hypocalcemia is done with 1 to 3 g of elementary cal-

cium per day in the various forms of salts available (table 2). Although calcium carbonate is the most used salt, it needs gastric acid so that it may be solubilized and absorbed, and causes more collateral gastrointestinal effects than other salts. (39). All patients with hypoparathyroidism or pseudohypoparathyroidism who become hypocalcemic must use vitamin D or analogous in addition to calcium (table 3). The vast majority of patients obtain control with calcitriol in dosages of 0.25 μ g, taken twice daily, up to 0.5 μ g four times daily. High doses of oral Cholecalciferol can also be used (50.000 to 150.000 UI/day), but the risk of intoxication after years of treatment is elevated due to their long half-life. Treatment objectives are to maintain free ionized calcium levels within the normal interval, to avoid hypercalciuria, and to suppress PTH levels in patients with pseudohypoparathyroidism. Hypoparathyroidism causes increased excretion of urinary calcium in relation to serum calcium and predisposes hypercalciuria, nephrolithiasis, and nephrocalcinosis. On the other hand, patients with pseudohypoparathyroidism that have low urinary calcium in relation to serum calcium may tolerate serum calcium levels within the normal interval without developing hypercalcemia. Vitamin D intoxication must be remembered in patients with hypercalcemic symptoms. Thiazide diuretics are used in cases of hypercalciuria and nonabsorbable antacid can be added to reduce hyperphosphatemia and prevent metastatic calcification. The product of *calcium x phosphate* must be kept below 55. Those patients must have their kidneys radiologically evaluated regularly in order to rule out nephrocalcinosis (4).

PTH₁₋₃₄ treatment has the advantage of normalizing calcemia without increasing calciuria, reducing the risk of nephrocalcinosis and renal insufficiency, and, theoretically, the antagonists of the calcium sensor receptor may be utilized in the treatment to promote the inactivation of the receptor and, consequently, increase PTH secretion, but there still have not been sufficient studies (40).

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Table 2. Most used calcium salt forms.

Salt	Element content	Milligrams of salt needed in order to obtain 1 g elementary calcium	Parenteral preparation
Calcium carbonate	40%	2500	
Calcium phosphate	38%	2631	
Calcium chloride	27%	3700	10% Solution= 273 mg/10 ml
Calcium citrate	21%	4762	
Calcium lactate	13%	7700	
Calcium gluconate	9%	11100	10% Solution= 93 mg/10 ml

Table 3. Vitamin D analogues.

	Calciferol D ₃ / D ₂	Calcidiol 25(OH)D	Calcitriol 1,25(OH) ₂ D	Alfacalcidol 1 α OHD
25-hydroxylation necessary	+	-	-	-
1 α -hydroxylation necessary	+	+	-	-
Physiological dose/dosage	2.5-10 μ g (1 μ g= 40 UI)	1-5 μ g (1 μ g= 40 UI)	0.25-0.5 μ g	1-3 μ g
Pharmacological dose/dosage	0.625-5 mg	20-250 μ g	0.5-3 μ g	1-3 μ g
Time needed to normalize calcium	4-8 weeks	2-4 weeks	3-7 days	7-14 days
Duration of effect	6-12 weeks	2-6 weeks	3-7 days	7-14 days

Table 4. Classification and clinical features of Pseudohypoparathyroidism subtypes.

	PHP1a	PHP1b	PHP1c	PHP2	PPHP
Hypocalcemia	Yes	Yes	Yes	Yes	No
OHA	Yes	No	Yes	No	Yes
Hormonal resistance	Multiple	PTH	Multiple	PTH	None
Response to IV PTH	No	No	No	Yes	Yes
G _s Mutation	Yes	No	No	No	Yes
Cause	G _s mutation	Non-methylation of promoter 1A	Unknown	Acquired defect?	Genomic imprinting

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