INTRODUCTION

Hypoparathyroidism is a metabolic disorder characterized by low serum calcium, increased serum phosphorus, and inadequate production of parathyroid hormone (PTH). Hypoparathyroidism can be broadly classified as postsurgical (75%) and nonsurgical (25%) in cause. When hypoparathyroidism is not the result of surgical removal of too much parathyroid tissue, inadequate circulating levels of PTH are usually the result of genetic, autoimmune, environmental, or other conditions that affect either parathyroid gland function or mass.1

KEYWORDS

- Medical hypoparathyroidism
- Autoimmune polyendocrine syndrome type 1 hypocalcemia
- Pseudohypoparathyroidism • Autosomal dominant hypocalcemia • Genetics
- Parathyroid hormone

KEY POINTS

- The causes of nonsurgical hypoparathyroidism are broadly classified as autoimmune (as part of the autoimmune polyendocrine syndrome type 1 or isolated) genetic variants, infiltrative, metastatic, radiation destruction, mineral deposition (copper or iron), functional (magnesium deficiency or excess), or idiopathic.
- Autoimmune polyendocrine syndrome1 is associated with circulating autoantibodies and infiltration of the involved organs with lymphocytes leading to organ failure and is characterized by 3 major clinical features (chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency); in addition, patients may have greater than 20 minor clinical features.
- Autoantibodies to 21-hydroxylase correlate with the development of adrenal insufficiency, and antibodies to NALP5 correlate with the development of hypoparathyroidism. A molecular diagnosis can be confirmed with DNA studies of the AIRE gene.
- Magnesium plays a key role in calcium homeostasis and should always be normalized.
The diagnosis of hypoparathyroidism is confirmed by the presence of a low concentration of serum or plasma calcium (total corrected for albumin or ionized) in the presence of a low or inappropriately normal level of PTH. The reduced PTH level leads to increased renal tubular phosphate reabsorption and, consequently, elevated serum phosphate levels. Hyperphosphatemia contributes to extraskeletal calcification with mineral deposition in the basal ganglia, cornea, renal parenchyma, as well as other tissues. Functional hypoparathyroidism develops in the presence of magnesium deficiency or excess. The evaluation and causes of nonsurgical hypoparathyroidism are reviewed in detail next.

Autoimmune Hypoparathyroidism

Autoimmune hypoparathyroidism is the most common cause of nonsurgical hypoparathyroidism. This condition can occur as an isolated feature or as a part of the autoimmune polyglandular syndrome type 1 (APS-I).

APS-I, also known as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED), is caused by mutations in the autoimmune regulator gene (AIRE), which is expressed in the lymph nodes, thymus, pancreas, adrenal cortex, and fetal liver.\(^2,3\) The inheritance is autosomal recessive; however, dominant transmission has been reported.\(^4,5\)

Chronic mucocutaneous candidiasis, hypoparathyroidism, and Addison disease represent the clinical hallmark of the syndrome; the clinical diagnosis of APECED requires the presence of at least 2 of these 3 major components. APECED typically presents in childhood with candidiasis, followed by hypoparathyroidism, which usually develops between 5 and 9 years of age and adrenal insufficiency during adolescence.\(^2,3,5,6\) More than 80% of patients with APS-1 exhibit hypoparathyroidism, which may be their sole endocrinopathy.

Minor components include greater than 20 organ-specific components.\(^7\) Genetic and environmental factors modify the phenotype resulting in diverse clinical presentations in the same family.\(^7\) A large range of autoantibodies may be present in APS-1, including organ-specific autoantibodies as well as antibodies to cytokines and interferons.\(^7-9\) Autoantibodies to intracellular enzymes restricted to specific organs in which the autoantigen is expressed can be measured and are useful for diagnostic screening.\(^10\) Assays for autoantibodies to 21-hydroxylase and to NACHT leucine-rich-repeat protein 5 (NALP5) can be helpful in predicting the development of adrenal insufficiency and hypoparathyroidism, respectively. Autoantibodies to cytokines may also be present\(^5\) as well as autoantibodies to type 1 interferon.\(^7,11\)

The molecular diagnosis of APS-1 can be confirmed by DNA analysis of the AIRE gene.\(^12\) The presence of minor components of APS-1 can be helpful in considering the diagnosis of APS-1. The minor features include keratitis, autoimmune hepatitis, primary ovarian insufficiency, enamel hypoplasia, enteropathy with chronic diarrhea or constipation, photophobia, periodic fever with rash, pneumonitis, nephritis, pancreatitis, and functional asplenia.\(^3,5\)

A diagnosis of APS-1 is strongly suggested by the presence of at least one of the major syndrome components and positive antibodies to type 1 interferon; sequencing of the AIRE gene can provide confirmation of the diagnosis.

The worldwide incidence of APS-1 is 1 per 100,000, but it is more commonly observed in 3 genetically isolated populations: Finns (incidence 1:25,000), Sardinians (incidence 1:14,000), and Iranian Jews (incidence 1:9000).\(^2,3\)

The association of AIRE mutations with isolated hypoparathyroidism is quite unusual. A kindred of 10 children, 3 of whom were diagnosed with hypoparathyroidism in the first decade of their life, were recently reported to have a mutation in the AIRE gene.
Only 1 of the 3 siblings with mutations in the AIRE gene developed additional features of APS-1 with the onset of premature ovarian failure at 33 years of age. The other 2 siblings (brothers) failed to develop any other clinical features of APS-1 even after 50 years of medical surveillance. Other investigators have confirmed that APS-1 can present with isolated hypoparathyroidism; however, follow-up has been of limited duration. Additional features of APS-1 can develop as late as the fifth decade of life. Another investigator described 2 children aged 4 years and 5 years with biallelic AIRE mutations and no other features of APS-1 apart from hypoparathyroidism. Two siblings with AIRE mutations have been reported with 1 brother aged 15 years demonstrating isolated hypoparathyroidism.

Antibodies to the calcium sensing receptor (CaSR) that activate signaling can suppress PTH secretion leading to hypoparathyroidism. Kifor and colleagues reported on 2 patients with activating anti-CaSR antibodies with direct functional actions on CaSR. One patient with long-standing hypoparathyroidism and Graves disease was noted to have a normal parathyroid gland at the time of subtotal thyroidectomy. The second patient was diagnosed with Addison’s disease and transient mild hypoparathyroidism. The hypocalcemia subsequently remitted indicating that there had not been irreversible destruction of the parathyroid glands. Antibodies against the extracellular domain of the CaSR are present in a subset of patients with isolated hypoparathyroidism. In one study, 14 of 25 patients with autoimmune hypoparathyroidism had circulating antibodies that were reactive to the extracellular domain of the CaSR. Antibodies to the parathyroid cell surface were present in 8 of 23 cases of idiopathic hypoparathyroidism. Other studies have shown varying rates of anti-CaSR antibody positivity. It is not yet clear whether the anti-CaSR antibodies play a causal role or serve as markers of tissue injury.

The management of an individual with APS-1 requires a multidisciplinary team at a specialized tertiary care center. Immediate family members, including the siblings, require further evaluation, including measuring autoantibodies for 21-hydroxylase, in order to determine the risk of developing adrenal insufficiency. Also measuring autoantibodies for NALP5 enables assessment of the risk of developing hypoparathyroidism. The management of hypoparathyroidism in APS-1 can be challenging if malabsorption is also present, as this may impact the absorption of calcium, cholecalciferol, as well as activated vitamin D.

**Infiltrative Causes**

Destruction of the parathyroid glands can occur secondary to granulomatous infiltration (eg, sarcoidosis, amyloidosis, Riedel thyroiditis); however, clinical hypoparathyroidism rarely occurs in these cases. There are a few case reports of possible infiltration of parathyroid glands by sarcoid granulomas leading to hypoparathyroidism. Autopsy studies have indicated a high frequency of amyloid deposits in the parathyroid glands. Several cases of hypoparathyroidism with Riedel thyroiditis have also been reported.

**Metastatic Cancer**

Pathologic involvement of the parathyroid glands resulting in hypoparathyroidism can rarely occur due to infiltrating metastatic cancer. However, metastases to the parathyroid glands are extremely rare with very few reported cases in the literature. In an autopsy study evaluating sites of metastases in 1000 patients with malignancy, no patient was found to have parathyroid metastasis, even though several unusual locations for metastatic deposits were identified. A prospective study of 160 consecutive necropsies in patients with various malignancies demonstrated metastatic
involvement of at least one parathyroid gland in only 19 cases. However, the same investigators in a retrospective study of 750 necropsies identified secondary malignant involvement of the parathyroid in 40 cases. The most common primary sites of malignancy with parathyroid metastases in decreasing order of frequency were breast, blood (leukemia), skin (malignant melanoma), lung, soft tissue (spindle cell sarcomas), and lymphomas.

**Radiation Destruction**

Another rare cause of hypoparathyroidism is exposure of the parathyroid glands to ionizing radiation. Radioactive iodine administered for the treatment of thyroid disease, particularly when high doses are given in the context of thyroid carcinoma, has been associated with hypoparathyroidism in reported cases. A transient decline in PTH was observed 6 months after radioactive iodine therapy in 19 patients undergoing thyroid remnant ablation. None of these patients were symptomatic despite low PTH and low serum calcium. External beam radiotherapy used for the treatment of thyroid cancer has not been documented to impact parathyroid gland function.

**Mineral Deposition**

Hypoparathyroidism may occur because of accumulation or deposition of minerals in the parathyroid gland. Wilson’s disease is among the rarest causes of hypoparathyroidism and results from destruction of parathyroid glands due to deposition of copper. This condition has been reported by a few investigators. Carpenter and colleagues described a 11-year-old girl with hypoparathyroidism secondary to Wilson’s disease. Fatima and colleagues described an affected 16-year-old boy. Okada and colleagues reported a case of Wilson’s disease associated with hypoparathyroidism and amenorrhea.

Hemochromatosis with iron overload, either primary or secondary, due to chronic transfusions (eg, in thalassemia) has also been associated with hypoparathyroidism. The mainstay of treatment of severe beta thalassemia is regular blood transfusions. Hypoparathyroidism secondary to iron overload has been reported to occur in 13.5% to 20.0% of the patients. There has been a decrease in the reported cases of hypoparathyroidism secondary to iron overload following introduction of improved chelation therapy regimen’s suggesting chelation may prevent the development of hypoparathyroidism.

**Toxic Agents**

Parathyroid tissue is highly resistant to chemotherapeutic and cytotoxic medications with the exceptions of L asparaginase, which has been associated with parathyroid necrosis and ethiofos a radio and chemo-protective agent that causes reversible inhibition of PTH secretion.

**Transient Hypoparathyroidism**

A transient form of hypoparathyroidism can occur in the context of severe burn injury as well as acute illness.

Children and adults who have sustained severe burn injuries can develop magnesium depletion (secondary to loss through the burn wound, abnormal intestinal secretion, and increased metabolic rate) hypocalcemia, and hypoparathyroidism. As discussed later, magnesium is an important cofactor in the production of cyclic adenosine monophosphate (cAMP) and inadequate magnesium levels block intracellular cyclic AMP generation in parathyroid cells impacting the secretion of parathyroid
Another possible mechanism for the development of hypoparathyroidism in burn injury is cytokine-mediated upregulation of the calcium-sensing receptor in the parathyroid glands resulting in hypoparathyroidism as well as urinary calcium wasting.51

**Functional (Magnesium Deficiency or Excess)**

Magnesium has a significant impact on parathyroid function and on the serum calcium level. Hypomagnesemia and hypermagnesemia can result in hypocalcemia and impair parathyroid function.

Both the magnesium ion (Mg$^{2+}$) and calcium ion (Ca$^{2+}$) activate the CaSR and affect PTH synthesis and secretion.52 Intracellular Mg$^{2+}$ is also involved in the activation of adenylate cyclase and in intracellular signaling of cyclic AMP.53 Activation of the CaSR by Mg$^{2+}$ results in stimulation of phospholipase C and A2 and inhibition of intracellular cyclic AMP formation with inhibition of PTH release.54 Activation of the CaSR in the kidney decreases paracellular sodium, calcium, and magnesium transport and results in a loss of these cations through the kidneys. Heterozygous activating mutations of the CaSR result in autosomal-dominant hypocalcemia (ADH). Activation of the CaSR in the parathyroid glands leads to inappropriately low PTH levels. These patients may present with symptoms of hypocalcemia including seizures or muscle spasms. The hypocalcemia in ADH is associated with hypomagnesemia in many affected patients.55 Salt and water loss due to inhibition of active transcellular sodium chloride reabsorption and a picture similar to Bartter’s syndrome can also be seen in ADH.56

Approximately 70% of filtered Mg$^{2+}$ is reabsorbed in the thick ascending limb of Henle loop (TAL) and is passively reabsorbed with calcium in a paracellular manner via specialized tight junctions. These tight junctions are composed of a specific set of proteins of the claudin family that allow selective passage of ions and seal the paracellular space for water and electrolytes. Claudin proteins claudin-16 and claudin-19 play a key role in regulating paracellular Ca$^{2+}$ and Mg$^{2+}$ transport.57 Mutations affecting these two proteins result in impaired paracellular reabsorption of both Ca$^{2+}$ and Mg$^{2+}$ causing familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNO).58 Patients with these mutations have hypomagnesemia and develop nephrocalcinosis in childhood due to the presence of hypercalciuria and often chronic renal failure by the second decade of life.59,60

Paracellular Ca$^{2+}$ and Mg$^{2+}$ transport in the TAL is regulated by the action of the basolaterally located CaSR. The CaSR senses extracellular Ca$^{2+}$ as well as Mg$^{2+}$ concentrations in the distal nephron as well as in other tissues and thereby plays an essential role in Ca$^{2+}$ and Mg$^{2+}$ homeostasis.57 PTH increases Mg$^{2+}$ reabsorption in the cortical TAL by enhancing paracellular permeability and also increases transcellular Mg$^{2+}$ reabsorption in the distal convoluted tubule (DCT).52,62 In the DCT only 5% to 10% of filtered Mg$^{2+}$ is reabsorbed, and this is via active transcellular Mg$^{2+}$ transport.58,63

Loss-of-function mutations in TRPM6 affect active transcellular Mg$^{2+}$ transport in both the kidney and the intestine and result in hypomagnesemia with secondary hypocalcemia (HSH). Familial HSH caused by mutations in transient receptor potential cation channel subfamily M member 6 (TRPM6) is an inherited disorder impairs intestinal magnesium absorption. The TRPM6 gene is involved in the formation of apical magnesium permeable ion channels in the intestine and kidney. Recessive mutations result in defective active transcellular magnesium uptake in the intestine and also impair renal magnesium conservation.64,65 Children with this mutation have severe

---

Medical Hypoparathyroidism

801

Downloaded for Anonymous User (n/a) at McMaster University - Canada Consortium from ClinicalKey.com by Elsevier on November 14, 2018. For personal use only. No other uses without permission. Copyright ©2018. Elsevier Inc. All rights reserved.
hypomagnesemia and seizures during infancy. In addition to hypomagnesemia, patients also have suppressed PTH levels with hypocalcemia. The severe hypomagnesemia leads to the suppression of PTH thought to be secondary to a block in PTH synthesis and secretion in the presence of profound hypomagnesemia. This paradoxical inhibition of the parathyroid involves intracellular signaling pathways of the CaSR with an increase in the inhibitory G alpha subunit activity. A resistance to PTH at the skeletal level is also seen in hypomagnesemia. Intracellular Mg$^{2+}$ is a cofactor of adenylate cyclase, and decreases in intracellular Mg$^{2+}$ contributes to the resistance to PTH.

The hypocalcemia in association with hypomagnesemia is resistant to treatment with Ca$^{2+}$ or vitamin D and requires Mg$^{2+}$ supplementation. Deficiencies in intracellular Mg$^{2+}$ may develop in the presence of a normal serum Mg$^{2+}$. Intracellular Mg$^{2+}$ may be a key regulator of serum PTH.

Hypomagnesemia may be due to decreased intake, decreased intestinal absorption, increased losses, or redistribution of Mg$^{2+}$. Common causes of hypomagnesemia are decreased absorption due to malabsorption, short bowel syndrome, severe vomiting, diarrhea, or steatorrhea.

Long-term proton pump inhibitor use contributes to enhanced gastrointestinal losses, most probably due to inhibition of TRPM6-mediated active transportation of Mg$^{2+}$ secondary to altered intestinal pH. However, the exact mechanism leading to hypomagnesemia still needs to be clarified.

The fractional excretion of magnesium (FEMg) enables us to determine if the magnesium deficiency is due to intestinal losses or due to renal wasting. The formula for FEMg is as follows: urine Mg \times plasma creatinine/plasma Mg \times urine creatinine \times 100\%, where Mg is magnesium.

An FEMg greater than 4% in the presence of hypomagnesemia is consistent with renal magnesium wasting.

An intestinal or nonrenal cause is likely to be present if FEMg is less than 2%. Low estimated glomerular filtration rate and severe hypomagnesemia can also lead to a reduced FEMg. A urinary magnesium excretion of more than 1 mmol/d in the presence of hypomagnesemia is consistent with renal magnesium wasting.

Drugs can cause hypomagnesemia by promoting renal magnesium wasting as listed below:

- Diuretics (thiazide and furosemide), antibiotics and antimycotics (foscarnet, amphotericin B, aminoglycosides, pentamidine, and rapamycin), anticancer agents (ie, platinum derivatives such as cisplatin, carboplatin), immunosuppressants (calcineurin inhibitors, such as tacrolimus and cyclosporine A), and also epidermal growth factor–receptor inhibitors (cetuximab).

- Hypermagnesemia may also cause hypocalcemia due to the inhibition of PTH release. Renal impairment decreases renal magnesium excretion and serum magnesium levels increase. Hypermagnesemia is also associated with an increased fractional excretion of Mg$^{2+}$ in order to maintain a normal serum Mg$^{2+}$. In familial hypocalciuric hypercalcemia, as well as with use of lithium, renal clearance of Mg$^{2+}$ is mildly impaired; hence, serum magnesium levels are higher than in other forms of primary hyperparathyroidism. Excess intake also results in high levels of serum magnesium (antacids, cathartics, laxatives, parenteral administrations of Mg$^{2+}$). Another important cause of clinically significant hypermagnesemia is the use of magnesium sulfate as a tocolytic therapy for eclampsia, which has been associated with hypocalcemia due to magnesium-induced suppression of PTH secretion.
Mitochondrial Disorders Associated with Hypoparathyroidism

Several mitochondrial disorders have been associated with hypoparathyroidism. These syndromes are caused by mutations and deletions in mitochondrial DNA and include the following:

Kearns-Sayer syndrome is a mitochondrial cytopathy that is characterized by encephalopathy, progressive external ophthalmoplegia, ptosis, retinitis pigmentosa, cardiomyopathy, cardiac conduction blocks, and ataxia.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome is a maternally inherited disorder caused by point mutations in mitochondrial transfer RNA. This syndrome usually manifests in childhood after a normal early development and affects the nervous system and muscles.

Mitochondrial trifunctional protein deficiency is a fatty acid oxidation disorder that manifests as nonketotic hypoglycemia, cardiomyopathy, hepatic dysfunction, skeletal myopathy, and developmental delays. In some cases, mothers of an affected fetus have acute liver degeneration during pregnancy.

Maternal Hyperparathyroidism/Hypercalcemia

The prevalence of primary hyperparathyroidism in the general population is 0.15%. It is more common in women, and 25% of cases of PHPT occur in women during the childbearing years. The true incidence during pregnancy, however, is not known; however, it is estimated that up to 80% of pregnant patients with primary hyperparathyroidism are asymptomatic, making the diagnosis of PHPT in pregnancy difficult. Complications associated with primary hyperparathyroidism in pregnancy have been reported to occur in up to 67% of mothers and 80% of fetuses. For the mother, hyperparathyroidism can present as hyperemesis, nephrolithiasis, and acute pancreatitis; in severe cases it may present as a hypercalcemic crisis. An infant who is exposed in utero to maternal primary hyperparathyroidism or hypercalcemia is at risk of having suppressed parathyroid function and hypocalcemia, which may lead to intrauterine growth retardation, preterm delivery, intrauterine fetal demise, or postpartum neonatal tetany if the mother remains untreated.

Idiopathic

The hypoparathyroidism can be confirmed as idiopathic in cause following a careful review of all the possible causes of hypoparathyroidism. Such individuals should continue to be closely followed and monitored to ensure that target organ damage is prevented.

SUMMARY

Nonsurgical hypoparathyroidism remains an important cause of hypoparathyroidism. It is essential to diagnose this condition early and determine the underlying cause. In young individuals or in the presence of a positive family history of consanguinity it is advised that the patient and the family be referred for genetic counseling. Appropriate DNA studies can also be completed enabling a molecular diagnosis. Treatment is advised to ensure that serum calcium is maintained in the low-normal reference range with close monitoring of calcium, phosphate, magnesium, as well as renal function. Patients require monitoring for the development of extraskeletal calcification as well as other complications of hypoparathyroidism.
REFERENCES


