PEDIATRIC HYPOPARATHYROIDISM

An introduction to hypoparathyroidism for patients, their families and friends, and healthcare providers

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Introduction

Parathyroid glands

There are usually four parathyroid glands located behind the thyroid gland in the lower front of the neck. The two inferior parathyroids (located in the lower poles of the thyroid gland) are derived from the endoderm of the 3rd pharyngeal pouch. The 4th pharyngeal pouch gives rise to the two superior parathyroids (located in the upper poles of the thyroid gland). The 3rd and 4th pharyngeal pouches are also responsible for the development of the thymus and a portion of the thyroid gland.

Parathyroid hormone

The chief cells in the parathyroid glands synthesize, store, and secrete parathyroid hormone (PTH). Secreted PTH is a protein of 84 amino acids (PTH [1-84]). PTH is metabolized by the liver (70%) and kidney (20%) and has a half-life (rate of disappearance from circulation) of 2 minutes [Bringhamurst et al, 2015].

Parathyroid hormone regulation

The parathyroid gland can respond rapidly to changes in blood calcium. There is a calcium-sensing receptor on the surface of the parathyroid cell that “senses” calcium availability. When there are low ionized (free) calcium concentrations in the blood, PTH is secreted by the chief cells in the parathyroid gland. PTH secretion can also be affected by magnesium concentrations. PTH provokes various responses within the body to help raise blood calcium levels. (See section on Targeted actions of PTH.) The eventual rise in blood calcium subsequently feeds back to the parathyroid gland to decrease production of PTH.

Targeted actions of PTH

PTH interacts with and mediates its action in the body through PTHR1, a G protein-coupled receptor, that is expressed in the bone and kidney. Binding of PTH to its receptor promotes cAMP production and activation of protein kinase A (PKA).

In the bone, PTH elicits a response that increases bone resorption. The resorption (break down) of bone results in the release of calcium and thereby helps raise blood calcium.

In the kidney, PTH triggers a few different responses: a) stimulates the conversion of vitamin D to its biologically active form, 1,25-dihydroxyvitamin D (calcitriol), that enhances absorption of dietary
calcium and phosphate in the intestine; b) promotes calcium reabsorption from the renal tubule back into the bloodstream; and c) encourages the removal of phosphate from the body through urinary excretion.

**What is hypoparathyroidism?**

Hypoparathyroidism occurs when there is not enough PTH in the body to maintain normal blood calcium levels. There are many different reasons why hypoparathyroidism develops. (See section on Causes of hypoparathyroidism.)

Hypoparathyroidism is a rare endocrine disorder. Prevalence estimates in the United States is 37 per 100,000 person-years [Clarke et al, 2016]. In other countries, reports range from 5.3 to 27 per 100,000 individuals [Bilezikian, 2020].

**Signs and symptoms of hypoparathyroidism**

Hypoparathyroidism can present with various symptoms that involve multiple organ systems (Figure 1). Most signs and symptoms are due to the imbalance of calcium and phosphate levels in the body.

**Causes of hypoparathyroidism**

**Genetic causes**

A number of essential genes involved in parathyroid gland development, PTH synthesis or secretion, and parathyroid gland destruction, have been identified. Genetic causes make up less than 10% of all hypoparathyroidism cases [Mannstadt et al, 2017]. There is greater likelihood for a genetic explanation of hypoparathyroidism when there is a young age of onset, family history of autoimmunity or consanguinity, or the presence of syndromic features [Clarke et al, 2016]. Among pediatric cases, genetic etiologies are a major cause of hypoparathyroidism.

Hypoparathyroidism may occur as part of syndromic conditions.

- The most common is DiGeorge syndrome (dysmorphic facies, cardiac defects, poor growth, thymic hypoplasia). Approximately 60% of children with hypoparathyroidism are diagnosed with 22q11.2 microdeletion syndrome (TBX1) [Kim et al, 2015]. DiGeorge syndrome type 2 (NEBL) harbors deletions in chromosome 10p [Daw et al, 1996].
- CHARGE syndrome (CHD7, SEMA3E; coloboma, heart defects, choanal atresia, growth retardation, genital and ear anomalies)
- HDR (hypoparathyroidism, deafness, renal dysplasia) or Barakat syndrome (GATA3)
- Sanjad-Sakati syndrome (TBCE) primarily affects Middle Eastern populations and is characterized by multiple dysmorphic features and severe growth retardation [Naguib et al, 2009].
- Hypoparathyroidism is seen in >50% of patients with Kenny-Caffey syndrome (TBCE, FAM111A), that presents with facial abnormalities, short stature, thickened bone dysplasia [Mannstadt et al, 2017].
- Mitochondrial diseases associated with hypoparathyroidism include Kearns-Sayre syndrome, Pearson Marrow-Pancreas syndrome, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes), mitochondrial trifunctional protein (MTP) deficiency syndrome (HADHB), and MCADD (medium-chain acyl-CoA dehydrogenase deficiency; ACADM) [Gordon et al, 2018].
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy or autoimmune polyglandular syndrome type 1 (APS1; AIRE) is characterized by mucocutaneous candidiasis (fungal infection of the skin, mucous membranes, nails), hypoparathyroidism, and adrenal insufficiency. Hypoparathyroidism develops due to autoimmune destruction of the parathyroid glands [Ferre et al, 2016].

Isolated hypoparathyroidism occurs due to mutations in transcription factors involved in parathyroid gland development (GCM2, SOX3), or the PTH gene that impairs synthesis, secretion, and binding of PTH to the PTH receptor.

Autosomal dominant hypocalcemia (ADH) results from gain-of-function mutations in CASR (type 1) or GNA11 (type 2) that suppresses PTH synthesis and secretion. In ADH1, increased urinary calcium and renal calcifications are a common feature. In ADH2, some patients have short stature.

Pseudohypoparathyroidism refers to a distinct group of disorders associated with PTH resistance and is beyond the scope of this booklet.

Acquired causes

Post-surgical hypoparathyroidism is the most common cause in adults and responsible for about 75% of all hypoparathyroidism cases [Clarke et al, 2016]. About 0.8% to 16.2% of individuals will develop permanent hypoparathyroidism after surgery [Cho et al, 2016; Edafe et al, 2014; Giordano et al, 2012; Lorente-Poch et al, 2015; Nawrot et al, 2014; Selberherr et al, 2015; Thomusch et al, 2003]. Hypoparathyroidism can develop due to surgical removal of the parathyroid glands or trauma to the glands during parathyroidectomy, thyroidectomy, or other neck surgeries. Vascular injury, infiltration (iron, copper, metastases), and radiation (rare) are other causes of hypoparathyroidism.

Other

Hypomagnesemia and hypermagnesemia from various causes can lead to functional hypoparathyroidism [Allgrove et al, 1984; Cholst et al, 1984].

Idiopathic

Some patients have no identifiable cause. These patients may have an autoimmune form of hypoparathyroidism [Bilezikian, 2020; Habibullah et al, 2018; Mannstadt et al, 2017].

Diagnosis of hypoparathyroidism

A detailed medical history, family medical history, and physical examination help identify patients at risk for hypoparathyroidism. When there is a clinical concern for hypoparathyroidism, laboratory tests are performed to confirm the diagnosis.

The laboratory hallmark of hypoparathyroidism is a low or inappropriately normal PTH at the time of hypocalcemia. In hypoparathyroidism, low calcium and PTH are accompanied by elevated phosphorus and low or normal 1,25-dihydroxyvitamin D concentrations. The excretion of calcium in the urine may be elevated [Mannstadt et al, 2017; Gafni et al, 2019] or low depending on the severity of hypocalcemia [Shoback, 2008]. Individuals with ADH1 have increased urinary calcium excretion despite low calcium concentrations in the blood.
Severe hypocalcemia can cause an abnormal heart rhythm (prolonged QT, torsade de pointes). If there is concern for this, an electrocardiogram is performed.

**Treatment of hypoparathyroidism**

**Calcium**

Hypocalcemia can be life-threatening. When hypocalcemia is severe and immediate action is required, intravenous calcium is administered in the hospital. Acute management requires monitoring for arrhythmia in addition to blood calcium levels.

Adequate oral calcium is necessary for long-term management of hypoparathyroidism.

- Dietary sources of calcium-enriched foods and beverages are encouraged (e.g., milk, yogurt, cheese). The recommended dietary intake of calcium is 700 mg/day for ages 1 to 3 years-old, 1,000 mg/day for ages 4 to 8 years-old, and 1,300 mg/day for ages 9 to 19 years-old.
- Additional calcium supplementation is often required. There are different formulations of calcium available. Calcium carbonate (40% elemental) requires an acidic gastric environment. Taking this supplement with meals helps absorption. Calcium citrate (21% elemental) can be taken on an empty stomach and is the preferred formulation for individuals with impaired gastric acid secretion or are taking medications that reduce gastric acid secretion (e.g., antacids, proton-pump inhibitors). More calcium citrate pills may be needed to provide the same amount of elemental calcium as calcium carbonate. For optimal absorption, calcium supplementation is divided into multiple, smaller doses throughout the day.

**Calcitriol**

The ability to make the active form of vitamin D (1,25-dihydroxyvitamin D) is diminished in hypoparathyroidism. Consequently, patients with hypoparathyroidism benefit from calcitriol, that increases intestinal absorption of calcium. Calcitriol may be prescribed once or twice-daily. The dosage is titrated to achieve a therapeutic blood calcium level. In most patients with hypoparathyroidism, the desired blood calcium concentration is in the lower range of normal, for instance, ~8-8.5 mg/dL.

**Sick day management**

Calcium needs increase during times of acute illness, hospitalization, and surgery. For this reason, patients are advised to closely monitor for symptoms, check blood calcium levels, and empirically increase their calcium and/or calcitriol doses until the illness resolves.

**Vitamin D**

Ergocalciferol and cholecalciferol are inactive forms of vitamin D. While the therapeutic benefit of these are less clear in the treatment of hypoparathyroidism, taking enough vitamin D to prevent vitamin D deficiency is sensible. A generally acceptable dose of vitamin D is 600 to 1,000 international units daily.

**Phosphate control**

Elevated serum phosphorus level in hypoparathyroidism is related to reduced ability by the kidneys to excrete phosphate. If reduction of serum phosphorus is indicated, this intervention is largely
based on reduction of the intestinal absorption of phosphorus by the use of phosphate binders, which when taken at mealtimes binds to dietary phosphate and allow it to pass through the gastrointestinal tract into the feces, or limitation of phosphorus content of the diet. Phosphate binders are broadly classified into calcium-based and non-calcium-based binders [Rastogi et al, 2020]. The calcium-based phosphate binders may also help maintain blood calcium, but when administered with food to achieve the intended binding to phosphorus, may have less benefit to raise serum calcium than when administered between meals due to sequestration in the gut as insoluble calcium phosphate. The non-calcium-based phosphate binders may be limited both by cost and gastrointestinal intolerance. However, the role of phosphate binder therapy or dietary phosphate restriction in the care of pediatric patients with hypoparathyroidism is uncertain [Gafni et al, 2019].

**Thiazide diuretics**

Hypercalciuria and calcium crystallization in the renal tubule or peritubular environment contribute to the renal manifestations of kidney stones and nephrocalcinosis. Urinary calcium excretion may be enhanced further by surges of serum calcium from calcium supplementation and calcitriol therapy. Thiazide diuretics (e.g., hydrochlorothiazide, chlorthalidone) combined with a low-salt diet can reduce urinary calcium excretion and may be considered adjunct therapy [Porter et al, 1978; Mannstadt et al, 2017; Gafni et al, 2019]. However, thiazide diuretics have not been systematically studied to demonstrate their safety and effectiveness as renoprotective therapies in pediatric hypoparathyroidism. Also, thiazide diuretics increase urinary magnesium and sodium losses so their use should be cautioned in patients with ADH and APS1 and adrenal insufficiency [Mannstadt et al, 2017].

**PTH analogues**

PTH analogues have the advantage over conventional treatment (calcium, calcitriol) to restore the physiologic actions of PTH on bone and the reabsorption of calcium in the kidney. Pediatric studies have demonstrated that PTH analogues successfully maintain stable blood calcium levels and normalize urine calcium excretion [Linglart et al, 2011; Winer et al, 2008; 2010; 2014; 2018]. PTH analogues are not FDA-approved for use in children.

**Complications of hypoparathyroidism**

**Hypocalcemia**

As a child grows, their calcium and calcitriol dosages may increase. Consistent adherence and supervision of prescribed treatment plans are certainly important. Frequent monitoring of symptoms and laboratory tests are recommended, particularly during illnesses and when treatment adjustments are actively being made.

**Hypercalcemia and hypercalciuria**

Excessive intake of calcium and calcitriol may lead to hypercalcemia and hypercalciuria.

**Kidneys**

Hypercalciuria is a feature of hypoparathyroidism due to reduced ability of the kidneys to reabsorb calcium from the urine, leading to crystallization of calcium in the peritubular tissues (nephrocalcinosis) or in the tubular environment (kidney stones). These complications may be seen in
approximately one-third of children with hypoparathyroidism [Levy et al, 2015]. Cumulative calcium deposition in the kidneys may ultimately lead to reduced kidney function; rates of chronic kidney disease in patients with hypoparathyroidism have been noted to be 2 to 17 times that of the age-matched general population [Mitchell et al, 2012], and 45% of children with hypoparathyroidism have been noted to have an abnormal estimated glomerular filtration rate (eGFR) in long-term follow-up [Levy et al, 2015].

Calcifications

Calcifications in the brain are seen in 52% to 74% of individuals with hypoparathyroidism [Goswami et al, 2012; Mitchell et al, 2012]. The precise cause and clinical significance of this finding is unclear. Brain imaging is done in the setting of unexplained neurological symptoms.

Normalizing the fasting phosphate (tolerating a slight elevation) and maintaining a calcium-phosphate cross-product < 55 mg²/dL² are advocated strategies to minimize ectopic calcifications in adults [Bollerslev et al, 2015; Brandi et al, 2016; Mannstadt et al, 2017]. However, the calcium-phosphate cross-product has not been extensively studied in pediatric hypoparathyroidism. The cross-product has not been shown to be a better predictor of ectopic calcification than serum calcium [O’Neill, 2007] and it does not correlate with 24-hr urine calcium excretion in children with genetic hypoparathyroidism [Winer et al, 2018].

Psychosocial considerations

Adults with hypoparathyroidism report a reduced quality of life with physical, emotional, and cognitive complaints. Optimizing calcemic control may help, but challenges remain [Santonati et al, 2015; Sikjaer et al, 2014; Tabacco et al, 2019; Vokes et al, 2018]. Pediatric studies are needed to understand the relationship between quality of life in hypoparathyroidism, laboratory values and its treatments.

Chronic hypoparathyroidism requires consistent medical attention and treatment. Also, managing a chronic disease may have negative consequences on the healthy development of youth. Stimulating play behavior in young children may augment their physical, emotional, cognitive, and social function while adapting to a chronic medical condition [Nijhof et al, 2018]. Child life specialists, psychologists, occupational therapists, and social workers are beneficial resources to offer psychosocial support, coping strategies, and strategies to overcome obstacles that might impair the healthy development of children.

References


