Hypoparathyroidism – disease update and emerging treatments

Hypoparathyroïdie : état des lieux et nouveaux traitements

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Abstract

Parathyroid hormone (PTH) is the primary regulator of blood calcium levels and bone metabolism. Insufficient levels of PTH lead to hypoparathyroidism, characterized by low serum calcium and elevated serum phosphate levels. It is most commonly caused by the inadvertent damage to the parathyroid glands during thyroid surgery. Patients with hypoparathyroidism are currently being treated with oral calcium and active vitamin D, and to avoid worsening hypercalciuria, target serum calcium levels are within the lower end of normal. With current treatment, patients may suffer from large swings in serum calcium and are at a substantial risk of chronic renal failure, nephrocalcinosis, and kidney stones. The recent FDA approval of recombinant human (rh) PTH(1-84) for the treatment of hypoparathyroidism adds PTH replacement therapy to the endocrinologist’s armamentarium to treat this chronic disease.

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Keywords: Hypoparathyroidism; Complications of therapy; rhPTH(1-84)

Résumé

L’hormone parathyroïdienne (PTH) est le principal régulateur du taux sanguin de calcium et du métabolisme osseux. L’insuffisance des taux de la PTH liée à l’hypoparathyroïdie se caractérise par une baisse des taux du calcium sérique et un niveau accru de phosphate sérique. L’hypoparathyroïdie est le plus communément liée à des altérations malencontreuses des parathyroïdes au cours de la chirurgie thyroïdienne. Les patients atteints d’hypoparathyroïdie sont actuellement traités par l’apport oral de calcium et des formes actives de vitamine D, et afin d’éviter l’aggravation de l’hypercalcurie, la cible des valeurs du calcium sérique est située dans la partie inférieure des normes. Avec les traitements actuels, les patients peuvent souffrir d’importantes fluctuations des calcémies, et courent un risque significatif d’insuffisance rénale chronique, de néphrocalcinose et de calculs rénaux. L’approbation récente par la FDA de la PTH recombinante humaine (rh PTH 1-84) dans le traitement de l’hypoparathyroïdie ajoute la substitution par la PTH à l’arsenal thérapeutique des endocrinologues pour traiter cette maladie chronique.

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1. Introduction

Parathyroid glands produce parathyroid hormone (PTH), a peptide hormone of 84 amino acids that is necessary for regulating blood calcium and phosphate levels, and for maintaining bone health. Parathyroid cells sense extracellular calcium through the G-protein coupled calcium sensing receptor (CASR) and respond appropriately with production and release of PTH when calcium is low, and suppression of PTH when it is high. PTH exerts its actions through binding and activation of the PTH/PTHrP receptor in the kidney and bone. PTH increases serum calcium by three main mechanisms: release of calcium from bone, stimulation of renal 1-alpha-hydroxylase which leads to an increase in active 1,25(OH)2-vitamin D, and reabsorption of calcium from the distal renal tubules. PTH also promotes renal phosphate excretion. Hypoparathyroidism is a life-long, orphan disease characterized by an inadequate production of PTH, resulting in low blood calcium levels (hypocalcemia) and elevated serum phosphate levels (hyperphosphatemia) [1,2].
2. Etiology of hypoparathyroidism

There are an estimated 60,000 patients with hypoparathyroidism in the United States [3]. The etiologies of hypoparathyroidism can be broadly categorized into postsurgical or medical causes.

2.1. Postsurgical

Postsurgical hypoparathyroidism is the most common form of the disease and comprises about 75% of patients [3]. During neck surgery, particularly total thyroidectomy, parathyroid glands can either be inadvertently removed, or their blood supply interrupted. Factors associated with this complication include the surgeon's experience, high-volume surgeons generally have improved outcomes, and the surgery itself since reoperation and extensive surgery carry a higher risk of complications [4]. Other risk factors include substernal goiter, Graves' disease, and cancer.

2.2. Medical

Medical causes of hypoparathyroidism comprise a diverse group of etiologies. Autoimmune hypoparathyroidism, the second most common cause of the disease, is caused by immune-mediated destruction of the parathyroid glands. It can occur sporadically, or as part of the inherited autoimmune polyglandular syndrome (APS) 1, also known as polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [3]. APS1 is an autosomal-recessive disorder resulting from a loss-of-function of the AIRE (autoimmune regulator) gene. The AIRE gene's product plays a crucial role in the development of tolerance towards self-antigens. When absent, tolerance to self-antigens is not correctly established, resulting in various autoimmune diseases. The classical clinical triad of APS1 consists of mucocutaneous candidiasis, Addison's disease, and hypoparathyroidism. Other autoimmune diseases may appear, such as type 1 diabetes, Hashimoto's thyroiditis, or celiac disease. The target of the autoimmune attack of the parathyroid glands is not clearly understood. Antibodies to the NACHT leucine-rich repeat protein 5 (NAPLP5) are often found in APS1 patients with hypoparathyroidism, yet the role of these antibodies has not yet been determined. Antibodies to the calcium-sensing receptor (CASR) have also been identified in a subgroup of patients with either APS1 or isolated autoimmune hypoparathyroidism [5]. Gene testing can identify AIRE mutations, but there is currently no validated clinical test for antibodies to establish the diagnosis of isolated autoimmune hypoparathyroidism.

Although genetic forms of hypoparathyroidism are rare, the identification of the causative genetic mutations, and subsequent elucidation of the mechanism by which mutated genes cause hypoparathyroidism, has greatly contributed to our understanding of parathyroid function and pathophysiology.

The genetic causes of isolated hypoparathyroidism can be grouped into three main categories according to the mechanism by which they lead to hypoparathyroidism. In the first group, patients develop parathyroid glands normally, but the secretion of parathyroid hormone at normal calcium concentrations is impaired. A prime example of this is autosomal-dominant hypocalcemia (ADH), caused by activating mutations in the calcium-sensing receptor [6,7]. ADH is the most common genetic form of hypoparathyroidism. More recently, gain-of-function mutations in the alpha subunit of G11, a signaling molecule downstream of the calcium-sensing receptor, were found to cause hypoparathyroidism as well [8–10]. In contrast, in the second group, patients do not develop parathyroid glands. This can be the result of mutations in transcription factors essential for parathyroid development, such as GCM2 [11–13]. Third, rare mutations in the PTH gene itself can cause incorrect processing and secretion of the hormone, leading to hypoparathyroidism [14].

Hypoparathyroidism can also be part of a complex genetic syndrome such as the DiGeorge syndrome (also known as 22q11 deletion syndrome), which is characterized by many deficits including immunodeficiency and congenital heart defects [15]. The hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome is caused by heterozygous mutations in the transcription factor GATA3 [16,17].

The hypoparathyroidism-retardation-dysmorphism syndromes (HRD) include the Kenny-Caffey, Sanjad-Sakati, and osteocraniostenosis syndromes. Mutations in the TCBE gene, a protein involved in microtubule assembly, and FAM111A have been identified in HRD [18].

3. Clinical manifestations

Most symptoms and clinical signs of hypoparathyroidism result from hypocalcemia. Classic presentations include neuromuscular irritability, which involves tingling of fingers and toes, perioral numbness, muscle cramps, laryngospasm and seizures [1,2]. Symptoms are influenced by the rate of the fall of serum calcium and the absolute degree of hypocalcemia. However, the clinical presentations vary a lot and while some patients have few symptoms with stable serum calcium values over years, others have erratic serum calcium concentrations, frequent occurrence of tetany, and renal complications.

A thorough history, including family history, often reveals the likely cause of the disease. Physical exam findings to look for include a surgical scar on the neck and findings suggestive of autoimmune disorders (Addison’s disease, vitiligo). A positive Trousseau’s sign is a very sensitive and specific physical finding in hypocalcemia. It is described as a painful carpal spasm or “main d’accoucheur” after inflating the blood pressure cuff above the systolic blood pressure for 3 minutes. Trousseau is present in 94% of patients with hypocalcemia and in only 1% of persons with normal calcium values [19]. A positive Chvostek sign, twitching of facial muscles in response to tapping over the area of the facial nerve, is less sensitive and specific. It is negative in 30% of hypocalcemic patients and positive in about 10% of normal people [20,21]. It is therefore recommended to check for the absence of Chvostek’s sign when a patient is normocalcemic and without symptoms.

The lack of PTH leads to low bone turnover [22], and dynamic histomorphometric indices demonstrate diminished
bone density and microarchitecture are markedly atypical. Areal bone density, measured by dual-energy x-ray absorptiometry (DEXA), is generally increased, especially at sites rich in trabecular bone [23,24]. Histomorphometric analysis reveals increased trabecular bone density, and 3-dimensional microcomputed tomography of iliac crest biopsies demonstrates unusual predominance of plate-like trabeculae [23]. Systemic studies of fracture incidence in hypoparathyroidism are lacking [25], and the clinical implications of the abnormal microarchitecture are a subject of debate.

Several other organs can be affected by hypoparathyroidism as well. In the cardiovascular system, hypocalcemia can lead to the prolongation of the QT interval on the electrocardiogram [26]. Cataracts can form in the eye, with affected patients predominantly suffering from cortical disease. [27]. Dental abnormalities such as hypoplastic teeth have been reported as well [28]. Patients with hypoparathyroidism often complain of fatigue, lack of energy, and anxiety. A case-control study reported higher anxiety scores in hypoparathyroid patients as compared to post-thyroidecotomy patients without hypoparathyroidism [27]. In an uncontrolled study of PTH(1-84) therapy, baseline quality of life in hypoparathyroid patients was reported to be diminished compared to normative data [29]. In a cross-sectional self-reporting study using a web-based questionnaire, patients reported that they felt unprepared to manage the disease and most felt that their physician does not understand the disease [30]. These results point to an empathy gap and the need for better education about hypoparathyroidism.

4. Conventional therapy

Conventional treatment of chronic hypoparathyroidism typically consists of oral active vitamin D (calcitriol or alphacalcidol), given once or twice a day, and oral calcium given several times a day in an attempt to increase serum calcium levels. Before the availability of active vitamin D, high dose ergocalciferol or cholecalciferol treatment was being used as treatment. Due to the long half-life of these drugs, inadvertent hypercalcaemia can result from high drug levels and can last for months, even after discontinuation of the medication, which puts patients at risk of renal toxicity.

Doses of calcium and active vitamin D needed to achieve acceptable serum calcium levels vary widely between patients [24]. Calcium and active vitamin D are titrated to balance two opposing goals: to minimize symptoms of hypocalcemia, while reducing the risk of hypercalcemia. Overtreatment can lead to hypercalcemia, since the action of PTH to increase renal reabsorption of calcium is absent. This balance however can be extremely difficult to achieve with this non-physiologic therapy. To achieve the right balance, target calcium levels are typically at the low-normal range (8.0–8.5 mg/dL). Occasional symptoms of hypocalcemia, such as mild tingling in fingers while exercising, can indicate that the patient’s serum calcium is indeed within target range.

Hyperphosphatemia is often ameliorated by the above treatment without additional intervention. If it persists, decreasing phosphate intake, administration of the calcium supplements with meals to bind phosphate, and increasing oral calcium while decreasing active vitamin D doses can sometimes be helpful.

There are no clinical guidelines for the management of hypoparathyroidism and no consensus on the follow-up of patients. The frequency of laboratory monitoring depends on several factors: we routinely measure serum calcium, albumin, and phosphate every 3–6 months, and we measure serum creatinine, and 24-hour urinary calcium excretion every 6–12 months.

5. Complications

Instead of simply replacing the missing hormone, PTH, affected individuals are currently given large amounts of oral calcium and active vitamin D analogs, treatments which, in addition to causing large swings in calcium, considerably increase the risk of renal damage (nephrocalcinosis, nephrolithiasis, and renal failure). In a study using a large patient registry, we found that even at Partners hospitals in Boston, Massachusetts, about 50% of patients with hypoparathyroidism suffer from renal failure or nephrocalcinosis [24]. Other pathological consequences include calcifications of basal ganglia in the brain [31].

6. Emerging treatments

Hypoparathyroidism was said to be the last classic endocrine deficiency disorder without approved replacement therapy. Similar to hypothyroidism (levothyroxine), diabetes (insulin) and Addison’s disease (cortisol), endocrinologists are used to replacing the missing hormone. Therefore, therapy with PTH for hypoparathyroidism should be the logical next step.

Conventional treatment with oral calcium and active vitamin D does not replace the function of PTH. For example, conventional therapy can worsen hypercalcemia, and does not correct low bone turnover and elevated calcium-phosphate product.

Human PTH(1-34), approved for the treatment of severe osteoporosis, has been studied for the use in hypoparathyroidism [32–38]. It is safe and increases serum calcium. Because of its relatively short half-life, PTH(1-34) is injected twice a day or given as a pump. However, no registration trial has been conducted, and PTH(1-34) is not approved for hypoparathyroidism.

By contrast, the full-length recombinant human PTH(1-84) has been studied in hypoparathyroidism [39–44], and a randomized, placebo-controlled phase 3 clinical trial has been performed for the registration of this treatment [45]. In January of 2015, the FDA approved rhPTH(1-84) (Natpara) for the treatment of hypoparathyroidism.

7. Conclusions

Management of hypoparathyroidism can be complex. Serum calcium can be improved with oral calcium and active vitamin D yet treatment requires a balance between achieving acceptable serum calcium concentrations and worsening hypercalcemia. Renal complications are often underestimated, and monitoring
urinary calcium excretion is an integral part of the management of hypoparathyroidism. With the recent approval of rhPTH(1-84), replacement therapy is now available and should contribute to an improved treatment of hypoparathyroidism.

Disclosure of interest

MM is member of a scientific advisory board to NPS Pharmaceuticals. ELM has no conflicts of interest to declare concerning this article.

References


