CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

# Hypoparathyroidism

Rachel I. Gafni, M.D., and Michael T. Collins, M.D.

*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

From the Skeletal Disorders and Mineral Homeostasis Section, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD. Address reprint requests to Dr. Gafni or Dr. Collins at the National Institutes of Health, 30 Convent Dr., MSC 4320, Bldg. 30, Rm. 228, Bethesda, MD 20892, or at gafnir@mail.nih.gov or mc247k@nih.gov.

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**A previously healthy 31-year-old woman began having progressive paresthesias and numbness of her hands, neck, face, and back, for which she was evaluated by her primary care physician and a neurologist, but no cause was identified. Her family history was notable for autoimmune thyroid disease in a parent and sibling and psoriasis in another sibling. Six months after the onset of symptoms, the patient had carpopedal spasms in her hands and feet during exercise, which rapidly progressed to difficulty breathing and full body tetany. On arrival at the emergency department, she was found to have hypocalcemia and hyperphosphatemia, with an undetectable parathyroid hormone level. How would you evaluate and treat this patient?**

## THE CLINICAL PROBLEM

*An audio version of this article is available at NEJM.org*

Hypoparathyroidism is a rare disorder of parathyroid hormone (PTH) deficiency, with an estimated prevalence of 23 to 37 cases per 100,000 person-years. It most commonly occurs as a complication of anterior neck surgery (in approximately 78% of cases) and is therefore seen more frequently in older adult women, who are more likely than others in the general population to undergo thyroid surgery.[1,2] However, there is an expanding list of genetic[3] and nonsurgical acquired causes, including autoimmune causes (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). PTH is critical for maintaining the level of circulating calcium within a narrow normal range through its actions on bone, kidney, and intestine. Its secretion is regulated primarily by the calcium-sensing receptor (CaSR) found on parathyroid chief cells; when ambient calcium levels are low, the CaSR is inactive and PTH synthesis and secretion are increased.[4] PTH then regulates calcium and phosphate levels by actions on the bone, kidney, and, indirectly, intestine (Fig. 1).

Most patients with hypoparathyroidism have neuromuscular signs and symptoms of hypocalcemia, ranging from mild paresthesias, muscle cramps, and prolongation of the corrected QT (QTc) interval to severe, life-threatening manifestations such as arrhythmias, laryngospasm, and seizures.[6] In some patients, particularly those with certain genetic forms of hypoparathyroidism, the hypocalcemia may be asymptomatic. Often a parent or older sibling is identified as having hypoparathyroidism after the diagnosis is made in a child.[7] Because there is a lack of PTH-mediated bone resorption, patients have low bone turnover, so over time, their bone mass increases.[8] However, the data on fracture risk among patients with this disorder vary. In some postsurgical hypoparathyroid cohorts, patients may have a decreased risk of fracture in the upper extremities,[9,10] whereas others have had an increased risk of vertebral fractures despite having normal or increased

Key Clinical Points

Hypoparathyroidism

- Hypoparathyroidism is a rare disease that results in hypocalcemia. Symptoms, when present, range from paresthesias and muscle cramps to seizures and laryngospasm.
- The most common cause is injury to or removal of the parathyroid gland during anterior neck surgery. Other genetic or autoimmune causes may be isolated or part of a larger syndrome.
- Hypoparathyroidism is often associated with basal ganglia calcification, cataracts, and neuropsychiatric symptoms.
- The goal of treatment is to maintain the blood calcium level near the low end of the normal range while preventing symptoms of hypocalcemia; this is usually achieved with oral calcium and active vitamin D (calcitriol or alfacalcidol) supplementation but may involve treatment with subcutaneous parathyroid hormone therapy.
- Treatment is commonly associated with hypercalciuria, nephrocalcinosis, nephrolithiasis, and renal insufficiency, thus emphasizing the need for careful monitoring and improved therapies.

bone mineral density.[11] In patients with hypoparathyroidism with a nonsurgical cause, who often have other risk factors for fracture such as use of glucocorticoids and anticonvulsant agents, the fracture risk may be increased.[12,13]

Patients with hypoparathyroidism may have increased risks of infection and cardiovascular disease.[9,14] Basal ganglia calcification, although of uncertain clinical significance, has been reported in more than 50% of patients with hypoparathyroidism of varying causes and is thought to be mediated, in part, by chronic hyperphosphatemia.[15,16] Cataracts are also a feature of long-standing nonsurgical hypoparathyroidism.[9,17] Patients with nonsurgical hypoparathyroidism may have dental abnormalities, including enamel hypoplasia and hypodontia.[18] Many patients have a reduced quality of life, with nonspecific symptoms that can include general fatigue, a lack of focus (often referred to as "brain fog"), depression, and other neuropsychiatric issues.[9,10] Renal complications frequently develop and appear to be related to therapy.

## Strategies and Evidence

### Prevention

Large epidemiologic studies have estimated that the overall incidence of hypoparathyroidism after anterior neck surgery is approximately 8%, with 75% of cases resolving within 6 months and the remaining 25% resulting in permanent hypoparathyroidism.[2,20] Postsurgical hypoparathyroidism is much less common when surgery is performed by experienced neck surgeons who perform at least 50 to 100 thyroidectomies or parathyroidectomies per year. At high-volume centers, hypoparathyroidism develops in less than 2% of patients undergoing these operations.[21] Additional predictors of permanent postsurgical hypoparathyroidism include extensive neck dissection, exploration on both sides of the neck, repeat neck surgery, a history of Graves' disease, an inability to visualize the parathyroid glands during surgery, a calcium level of less than 7.5 mg per deciliter (1.88 mmol per liter) 24 hours after surgery, and postoperative bleeding resulting in additional surgery.[21,22] After surgery, close monitoring of calcium and PTH levels is indicated in order to identify hypoparathyroidism before the development of severe, symptomatic hypocalcemia. Rarely, hypoparathyroidism can develop years after surgery.[23]

### Diagnosis and Evaluation

Hypoparathyroidism is suspected in patients with a low ionized or albumin-corrected blood calcium level, hyperphosphatemia, and an intact PTH level that is low or that is inappropriately in the normal range. When the blood calcium level is low, the intact PTH level would be expected to be elevated. In patients who have not undergone neck surgery, the differential diagnosis of hypoparathyroidism is broad and can be subdivided into disorders of parathyroid gland formation, parathyroid hormone secretion, and parathyroid gland destruction (Table S1 in the Supplementary Appendix).

Although genetic disorders typically become apparent in childhood, subtle manifestations of hypoparathyroidism may be missed, particularly if hypocalcemia is mild or intermittent. For example, the incidence of chromosome 22q11.2 deletion syndrome is 1 case per 3000 live births, and hypoparathyroidism of varying severity is present in approximately half the affected per-

pregnancy.[50] Hypocalcemia may promote preterm labor and put the neonate at risk for hyperparathyroidism. For this and other reasons, hypoparathyroidism during pregnancy should be considered a high-risk state.[50]

### PHARMACOTHERAPY

More data are needed to inform long-term benefits and risks of PTH 1–84 therapy as compared with conventional therapy. Small, short-term, crossover studies have suggested that continuous subcutaneous PTH 1–34 infusions delivered by pump may be more physiologic than injections.[51] Long-acting PTH analogues,[52] PTH-related protein analogues,[53] PTH receptor modulators,[54] and antagonists of the CaSR (calcilytics)[55] are all in various stages of development; study is needed to assess their potential roles in practice.

## GUIDELINES

The European Society of Endocrinology[32] and the First International Conference on the Management of Hypoparathyroidism[33] have published management guidelines. The American Thyroid Association published a statement on the diagnosis, prevention, and management of postoperative hypoparathyroidism.[22] The majority of the recommendations in these guidelines are based on expert opinion and small studies rather than on large, controlled trials. The recommendations in this review are generally consistent with these guidelines.

## CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has new-onset hypocalcemia consistent with hypoparathyroidism. Urgent treatment with intravenous calcium (calcium gluconate, if administered through a peripheral intravenous catheter) is appropriate. We would also promptly initiate oral calcium carbonate and calcitriol therapy in divided doses to minimize symptoms of hypocalcemia and to maintain an albumin-adjusted blood calcium level near the low end of the normal range and 24-hour urinary calcium excretion in the weight-adjusted normal range. If treatment with calcium and calcitriol was ineffective at controlling symptoms of hypocalcemia, we would consider treatment with PTH 1–84, as well as calcium and vitamin D supplementation as needed. The patient's strong family history of autoimmunity suggests an autoimmune cause of hypoparathyroidism and necessitates screening and surveillance for other autoimmune disease in this patient.

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