

Multiple Endocrine Neoplasia Syndrome: Asymptomatic Primary Hyperparathyroidism: A perspective Study

Wael El-Adl, Kreiter Serge, Henrik Suttman, Rania Farouk el-Sayed, A M Attia

Department of Endocrinology, Egypt.

Corresponding Author : Wael El-Adl, Department of Endocrinology, Egypt. Email: waelalimahaer@hotmail.com

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Abstract

Hyperparathyroidism is a common condition that affects 0.3% of the general population. Primary and tertiary care specialists can encounter patients with primary hyperparathyroidism, and prompt recognition and treatment can greatly reduce morbidity and mortality from this disease. In this paper we will review the basic physiology of calcium homeostasis and then consider genetic associations as well as common etiologies and presentations of primary hyperparathyroidism. We will consider emerging trends in detection and measurement of parathyroid hormone as well as available imaging modalities for the parathyroid glands. Surgical indications and approach will be reviewed as well as medical management of primary hyperparathyroidism with bisphosphonates and calcimimetics.

Introduction

Parathyroid hormone is the chief regulator of calcium homeostasis in the human body. Primary hyperparathyroidism (PHPT) results from inappropriate overproduction of parathyroid hormone from one or many parathyroid gland(s) and presents with hypercalcemia. It is the third most common endocrine disorder affecting 0.3% of the general population, 1%–3% of postmenopausal women and a total population incidence of 21.6 cases per 100,000 person-years PHPT usually occurs as the result of sporadic parathyroid adenomas or carcinomas but can also be seen in association with multiple endocrine neoplasias and in rare genetic syndromes and metabolic diseases.

In children, primary hyperparathyroidism is rare. The most common cause is parathyroid adenoma, usually due to single gland disease, but severe neonatal hyperparathyroidism can also occur due to biallelic mutations in the calcium sensing receptor gene (*CASR*) with hypocalciuric hypercalcemia.

It is important to differentiate primary from secondary and tertiary hyperparathyroidism. Secondary hyperparathyroidism occurs as a normal response to hypocalcemia due to diseases affecting the kidney (such as renal tubular acidosis), liver, intestines, and vitamin D deficiency. In newborn infants, maternal hypoparathyroidism with hypocalcemia, maternal pseudohypoparathyroidism, and rare genetic and metabolic syndromes can lead to secondary hyperparathyroidism. Tertiary hyperparathyroidism occurs in patients with long-standing secondary hyperparathyroidism who develop autonomous PTH production with hypercalcemia. The most common situation resulting in tertiary hyperparathyroidism is the patient with secondary hyperparathyroidism with renal failure who then receives a renal allograft this paper will focus on primary hyperparathyroidism.

Physiology of Calcium Regulation

Precise regulation of extracellular and intracellular calcium is essential for normal physiological processes such as cell signaling, neural function, muscular function (including cardiac contractility), hormone release and regulation, and bone metabolism [14]. Parathyroid hormone increases receptor-mediated tubular reabsorption of calcium in the kidney, stimulates release of skeletal calcium stores,

upregulates 1- α -hydroxylase leading to increased 1,25-dihydroxy-vitamin D production and increased calcium reabsorption from the gastrointestinal tract.

Diagnosis of Primary Hyperparathyroidism

Primary hyperparathyroidism is diagnosed when PTH is elevated, in the context of hypercalcemia, in a patient with no history of renal disease. This is usually a result of inappropriate parathyroid hormone secretion from one or more of the parathyroid glands. Biochemical measurement of -intact or -total PTH is performed through immunoradiometric (IRMA) and immunochemiluminescent assays.

Differential Diagnosis of Elevated PTH

Parathyroid hormone elevation can occur due to causes other than PHPT in patients with normal blood calcium levels. The most common cause is chronic kidney disease, but other causes include vitamin D deficiency, medications (such as lithium and thiazide diuretics), and familial hypocalciuric hypercalcemia (FHH) due to a heterozygous mutations of the calcium sensing receptor (*CASR*) gene. The latter can be reasonably differentiated from PHPT based on the calcium to creatinine clearance ratio of less than 0.01 (mmol: mmol) with 85% sensitivity and 88% specificity Vitamin D levels should be obtained in all patients with increased PTH levels and normal blood calcium levels since vitamin D deficiency can result in calcium levels which are lower than expected in patients with primary hyperparathyroidism.

Management of Primary Hyperparathyroidism

Surgical Management

The only cure for primary hyperparathyroidism due to parathyroid adenomas is surgical resection of the culprit gland or glands. In 2008, The Third International Workshop on Asymptomatic Primary Hyperparathyroidism revised the indications for surgery in asymptomatic patients—these include age less than 50 years, serum calcium 0.25 mmol/L above the upper limit of normal, creatinine clearance <60 mL/min, DXA t-score <-2.5 at any site, and/or previous fragility fracture

Identification of Suspect Hyper secreting Parathyroid Glands

If a surgeon is planning an open parathyroidectomy, where all 4 glands are directly visualized, no preoperative imaging may be required and the use of preoperative imaging in such circumstances is a matter of personal preference for the surgeon. However, preoperative imaging is needed if the surgeon is planning minimally invasive parathyroidectomy, where only one side of the neck is exposed. Preoperative imaging can also be helpful in patients with previous neck surgery in whom scar tissue can make direct visualization more challenging.

Methods

Of the 42 patients (38 had MEN 1 syndrome; 4 had MEN 2A syndrome), 40 patients were treated surgically: 29 had initial parathyroidectomy at UCSF; 11 were referred to UCSF because of MEN syndrome. Eight of these 11 patients required reoperation for persistent or recurrent hyperparathyroidism. Patients with hyperplasia were treated with subtotal parathyroidectomy; the glands of those patients with solitary or double adenomas were removed with or without biopsy of the normal appearing glands.

Results

Overall, in seven (50%) of 14 patients with hyperplasia, three (16%) of 19 patients with solitary adenoma, and one (14%) of seven patients with double adenomas, recurrent or persistent hyperparathyroidism developed. Failure in patients with hyperplasia was due to missed supernumerary glands (13%) and missed ectopic glands (33%). Failure occurred in patients with solitary (three patients) or double (one patient) parathyroid tumors because of unrecognized hyperplasia. None of the four patient with MEN 2A syndrome had persistent or recurrent disease, but hypoparathyroidism developed in one patient; hypoparathyroidism developed in three patients with MEN 1 syndrome.

Conclusions

These data suggest that although many patients with primary hyperparathyroidism and MEN syndrome have multiple abnormal parathyroid glands, two populations of patients exist; one population has solitary or double adenomas and recurrence is uncommon, whereas the other population of patients has hyperplasia and persistent or recurrent disease is common.

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