Primary Hyperparathyroidism

This department covers selected points from the 2008 Endocrine Update: A CME Day from the Division of Endocrinology and Metabolism at McMaster University and the University of Western Ontario.
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Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in the outpatient clinical setting.[1] This condition can occur at any age but mainly affects persons > 50-years-old and post-menopausal women.[1,2]

Etiology and associated conditions

The chief cells of the parathyroid glands secrete parathyroid hormone (PTH) in response to low serum calcium levels, PTH mobilizes calcium by enhancing renal calcium reabsorption, stimulating osteoclast-mediated bone resorption and catalyzing the conversion of 25-hydroxyvitamin D3 to 1,25 hydroxyvitamin D3 (25-OHD) which, in turn, stimulates calcium reabsorption from the GI tract.[3]

PHPT is characterized by elevated serum calcium in the setting of an elevated or normal PTH. Eighty-five per cent of PHPT cases are caused by a sporadic PTH-secreting solitary adenoma of parathyroid chief cells. Multi-glandular hyperplasia and a parathyroid carcinoma account for approximately 15% and approximately < 1% of PHPT cases, respectively.[4]

PHPT is also associated with rare familial disorders that include multiple endocrine neoplasia (MEN) type 1 and type 2A syndromes, familial hypocalciuric hypercalcemia (FHH), familial hyperparathyroidism-jaw tumour syndrome, neonatal severe hyperparathyroidism or familial isolated hyperparathyroidism.[1] FHH, a benign cause of hypercalcemia, mimics PHPT and is caused by an inactivating mutation of the calcium-sensing receptor which makes the receptor less sensitive to calcium in the parathyroid glands and the kidneys.[5,6] Thiazide diuretics may unmask underlying PHPT as they cause mild hypercalcemia by reducing urinary calcium excretion.[7]

Eleanor's Case

Eleanor, a 55-year-old school teacher, is in your office to review her blood work. Her total calcium is 2.78 mmol/L and parathyroid hormone (PTH) is 12 pmol/L. Her past medical history includes hypertension for which she takes a thiazide diuretic and an ARB. She reached menopause at age 52 and has not taken hormone replacement therapy. She is a lifetime non-smoker and consumes alcohol occasionally. She has no history of nephrolithiasis or fragility fractures. She feels well otherwise but sometimes misses work due to vague symptoms of fatigue. Her review of systems and physical examination are unremarkable.

What further investigations need to be ordered?

Does she have primary hyperparathyroidism (PHPT)? If PHPT is confirmed, is this patient a candidate for parathyroid surgery or can she be followed with medical surveillance?

Read on for the answers to Eleanor's case.

Eleanor's Case cont'd...

Eleanor's thiazide diuretic should be discontinued and optimal BP control could be achieved with other antihypertensives. Repeat measures of serum calcium and PTH should be ordered after stopping the thiazide diuretic. Other investigations include renal function tests, 24-hour urinary calcium excretion, urinary calcium/creatinine ratio, 25-OHD and a dual energy x-ray absorptiometry (DEXA) scan for evaluating BMD. Eleanor should also be screened for secondary causes of hypercalcemia. If PHPT is confirmed, further discussion with the patient is needed regarding medical or surgical management.

Diagnosis of PHPT

Clinical features

Patients with PHPT may present with:

- symptomatic hypercalcemia,
- asymptomatic hypercalcemia detected incidentally, or
- normocalcemic hyperparathyroidism.

Symptomatic hypercalcemia is more common in developing countries where biochemical screening is not widely available to the majority of the population. The patients in such countries usually present with more advanced disease and may have debilitating renal and skeletal complications of hyperparathyroidism at initial presentation of PHPT.[8] The spectrum of bone disease in symptomatic PHPT may include bony pain, low BMD greatest at cortical skeletal sites, fragility fractures or rarely primary hyperparathyroid bone disease (osteitis fibrosa cystica). Renal manifestations include nephrolithiasis, nephrocalcinosis and renal insufficiency. Patients with PHPT may have GI symptoms of nausea, vomiting, peptic ulcer disease, constipation and pancreatitis. Neuropsychiatric disturbances vary and include lethargy, decreased cognitive and social function, depressed mood, psychosis and coma.[9] Patients with PHPT may also have left ventricular hypertrophy and a shortened QT interval.[10]

The classical presentation of PHPT with "bones, stones and abdominal groans" is now uncommonly seen in the western world. Most patients in the developed countries have asymptomatic forms of PHPT or nonspecific symptoms such as fatigue, mild depression or cognitive impairment. Less commonly, asymptomatic PHPT may present as normal serum calcium levels with elevated PTH, which is termed "normocalcemic PHPT." These patients may initially present for evaluation of low BMD, osteoporosis or a fragility fracture.[11] On physical examination, there are no specific findings of asymptomatic PHPT and parathyroid adenomas or carcinomas are rarely palpable.

Laboratory findings

PHPT is diagnosed when intact PTH is elevated or high normal in the setting of elevated total or ionized calcium levels. The main goal of further laboratory testing is to rule out other etiologies of hypercalcemia. Findings suggestive of FHH include a urinary calcium/creatinine clearance ratio < 0.01. It is important to distinguish FHH from asymptomatic hyperparathyroidism because a parathyroidectomy does not cure the condition. Evaluating serum and urinary calcium in the family members of the patient is helpful in confirming the diagnosis, however DNA analysis for mutations in the calcium sensing receptor

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gene can be completed if a *de novo* case is suspected. Vitamin D insufficiency can also present in a similar manner to FHH and can be associated with lower urinary calcium excretion. Renal function tests may indicate the extent of kidney involvement in the hyperparathyroid state. In patients who present with a family history of multiple endocrine tumours, genetic testing for mutations in the menin and RET gene is considered.

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Management of PHPT—surgical and medical

The definitive therapy for symptomatic PHPT is a parathyroidectomy. The type of preoperative imaging and surgical techniques for a parathyroidectomy are best decided in consultation with an experienced surgeon. Imaging is of value prior to surgery and is not used as a diagnostic tool.

In patients with asymptomatic PHPT, medical management is a suitable option if there is mild hypercalcemia, relatively well maintained skeletal and renal status, contraindications to surgery or other factors such as patient preference.[12] Bisphosphonates, in particular alendronate and hormone replacement therapy (HRT), have been shown to decrease bone turnover and increase BMD in PHPT. It is not known whether these treatments also reduce fracture risk. Bisphosphonates may be the agent of choice due to concerns of HRT related to CVD and breast cancer. Raloxifene, a selective estrogen receptor modulator, decreases bone turnover but more research is needed to elucidate its effects on BMD. Bisphosphonates, HRT and raloxifene do not significantly lower serum calcium or PTH levels. A calcimimetic agent, cinacalcet, reduces both serum calcium and PTH levels but has not been shown to improve BMD. Cinacalcet is not routinely used for PHPT and its use is generally limited for treating symptomatic hypercalcemia in consideration for surgery.[13]

Patients should also be advised to avoid factors that exacerbate hypercalcemia such as immobilization and intravascular volume depletion which can precipitate a hypercalcemic crisis. Dx

For references, please contact **diagnosis@sta.ca**