Evaluating Primary Hyperparathyroidism

What to Look for in Family Practice

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John's Case

John is a 74-year-old man with hypercalcemia. He was previously on hydrochlorothiazide, which was discontinued. Off of hydrochlorothiazide, he continues to have hypercalcemia with an ionized calcium of 1.59 mmol/L, total calcium of 2.88 mmol/L, and an elevated parathyroid hormone (PTH) of 9.50 pmol/L. Magnesium, phosphate, and 25-hydroxy vitamin D_3 are normal at 0.72 mmol/L, 0.99 mmol/L, and 89 nmol/L, respectively.

Read on for more on John.

What is primary hyperparathyroidism?

Primary hyperparathyroidism is the most common cause of hypercalcemia in the ambulatory setting. It usually affects people over the age of 50 and is more common in postmenopausal women.[1,2] Parathyroid hormone is secreted by the chief cells of the parathyroid gland in response to decreasing serum calcium, which regulates calcium homeostasis. PTH enhances renal tubular calcium absorption, osteoclast-mediated bone resorption, and calcium absorption in the bowel through the conversion of 25-hydroxy vitamin D_3 to 1,25-hydroxy vitamin D_3.[3]

What causes primary hyperparathyroidism?

Most cases of primary hyperparathyroidism are caused by a solitary PTH-secreting adenoma of the chief cells in the parathyroid gland; multiglandular parathyroid hyperplasia is less common.[1] Parathyroid carcinoma is present in less than 1% of cases.[3]

Primary hyperparathyroidism may also occur in genetic disorders, including multiple endocrine neoplasia (types 1 and 2A), familial isolated hyperparathyroidism, and familial hypocalciuric hypercalcemia.[3] The latter is caused by an inactivating mutation in the calcium-sensing receptor gene, which is inherited in an autosomal dominant fashion. The receptor becomes less sensitive in the parathyroid gland and kidneys, resulting in inappropriately elevated PTH in the face of hypercalcemia as well as decreased renal clearance of calcium.[4,5]

Certain drugs may also contribute to altered calcium homeostasis as thiazides reduce urinary calcium excretion, leading to mild hypercalcemia, and lithium decreases the sensitivity of the calcium-sensing receptor.[6,7] The most common causes of secondary hyperparathyroidism are chronic renal failure and low levels of vitamin D.

Table 1: Investigations Required to Confirm Primary Hyperparathyroidism

- PTH
- Total calcium corrected for albumin
- Ionized calcium
- Phosphate
- Magnesium
- 25-hydroxy vitamin D_3
- Creatinine
- 24-hour urine creatinine
- 24-hour urine calcium

Back to John

John's 24-hour urine collection found his urine calcium to be 2.4 mmol/day and his urine creatinine to be 11.2 mmol/day. As John's serum creatinine was 77 µmol/L (*i.e.*, 0.077 mmol/L) and total calcium was 2.88 mmol/L, the calcium to creatinine clearance ratio was low at 0.0057. John then underwent calcium-sensing receptor DNA analysis and was subsequently diagnosed with familial hypocalciuric hypercalcemia. His daughter also has hypercalcemia with a similar lab profile and should be assessed for this mutation as well.

What are the symptoms of primary hyperparathyroidism?

Patients may present with symptoms of PTH excess or may be asymptomatic with hypercalcemia found incidentally. Symptoms include fragility fractures, low bone density, recurrent nephrolithiasis, nephrocalcinosis, and polyuria. Other symptoms of hypercalcemia include nausea, constipation, pancreatitis, depression, lethargy, and decreased mental functioning.[3]

It is important to exclude other causes of hypercalcemia, particularly if PTH is not elevated (see Table 1 for a list of investigations). The differential diagnosis of hypercalcemia includes granulomatous disease, cancer, medications, vitamin D intoxication, adrenal insufficiency, hypothyroidism, immobilization, and chronic renal failure. Parathyroid adenomas are rarely palpable on physical examination.[3]

With primary hyperparathyroidism, serum calcium is raised and PTH is elevated or non-suppressed. Total serum calcium should be corrected for albumin, and ionized calcium should be measured along with 25-hydroxy vitamin D_3, phosphate, and magnesium. Evaluating the urinary calcium to creatinine ratio (see Table 2) will help to distinguish between primary hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH). In FHH, the ratio is usually less than 0.01, while, in primary hyperparathyroidism, this ratio will be greater than 0.01.[8]

Table 2: Calculating the Calcium to Creatinine Clearance Ratio

$$\frac{\text{24-hour urine calcium (mmol/day)} \times \text{serum creatinine (mmol/L)}}{\text{24-hour urine creatinine (mmol/day)} \times \text{total serum calcium (mmol/L)}}$$

How should primary hyperparathyroidism be investigated?

Patients should be asked about symptoms of hypercalcemia and any history of neck irradiation. Medications, especially thiazides and lithium, should be reviewed.

Especially in the hypertensive patient, multiple endocrine neoplasia should be considered with investigations for 24-hour urine catecholamines and metanephrines, prolactin, chromogranin A, and gastrin.

Chronic kidney disease can lead to secondary increases in PTH, so renal function should be assessed. Evaluation of bone mineral density is also useful.[3]

How is primary hyperparathyroidism treated?

Primary hyperparathyroidism may be treated surgically though medical therapy may be indicated for select patients and those who do not meet guidelines for surgical intervention. Medical options include bisphosphonates or a calcimimetic agent.[3] No treatment is typically required for FHH.

Take-home Messages

- Primary hyperparathyroidism is a common cause of hypercalcemia in patients over 50 and postmenopausal women
- Most cases are due to a PTH-secreting adenoma though other familial disorders, such as multiple endocrine neoplasia and FHH, are possible
- It is important to rule out other causes of hypercalcemia, including cancers, granulomatous diseases, and medications
- The calcium to creatinine clearance ratio can distinguish between primary hyperparathyroidism and FHH

References
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