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AMPATHCHAT

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Primary Hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is a disorder of mineral metabolism characterised by incompletely (PTH) regulated, excessive secretion of parathyroid hormone (PTH) from one or more of the four parathyroid glands. It is usually first suspected on the basis of an elevated serum calcium concentration (corrected for the albumin level), or symptoms thereof – the so called "bones, stones, moans and groans syndrome" (Table 1).

The disorder is mostly benign with a single adenoma (80%) or multiple gland disease (20%). Parathyroid carcinoma is rare, accounting for <1% of all cases of PHPT. PHPT is characterised by hypercalcemia and levels of PTH that are inappropriately high for the hypercalcaemic state.

Table 1: Clinical features

Symptoms related to hypercalcaemia	Polyuria, polydipsia, constipation, anorexia, vomiting, dehydration, arrhythmias and altered mental status
Renal involvement	Hypercalciuria, nephrolithiasis, nephrocalcinosis, and/or reduced renal function
Skeletal involvement	Any combination of fragility fractures, skeletal deformities and bone pain (due to osteitis fibrosa cystica)

A familial syndrome should be considered when primary hyperparathyroidism is diagnosed at an early age (under 50 years), or there is a family history of hypercalcaemia, pituitary adenomas, pancreatic islet cell tumors, pheochromocytomas, or medullary thyroid cancer (Table 2).

Table 2: Risk factors

Non modifiable:	Environmental/modifiable:
• Gender: 2–3 times more common in women than in men • Age: most common in ≥50–60 year age group • Genetic (10% of cases): MEN syndrome types 1 and 2A	• Chronic low calcium intake • Reduced physical activity • Higher body weight or BMI • External neck radiation • Lithium therapy • Thiazide therapy

Presentation

The classic laboratory presentation of PHPT of increased serum corrected calcium with a concurrent increased PTH is found in approximately 75% of cases. However, these findings may also occur with lithium or thiazide use, tertiary hyperparathyroidism associated with end-stage renal failure, and familial hypocalciuric hypercalcaemia (FHH). In the remaining 25% of cases, increased calcium and normal PTH levels will be found (20%) and much less frequently, normal calcium levels and increased PTH levels (so-called normocalcaemic hyperparathyroidism, see below). A PTH level within the normal range, in the presence of hypercalcaemia, is considered inappropriate and still consistent with PTH-dependent hypercalcemia. PTH levels should be low in patients with PTH-independent hypercalcemia. In Figure 1, patients in "Confusion Area A" are those with high calcium levels with normal PTH levels. Minimally elevated or normal PTH (but inappropriately normal given the hypercalcaemia) could also be due to the rare FHH.

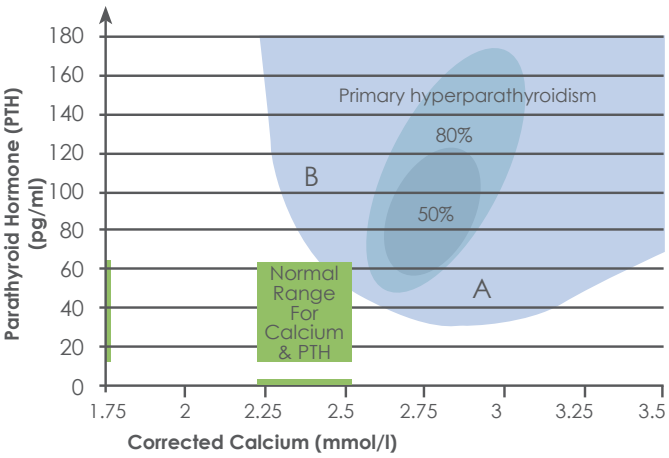

Figure 1: Interpretation of PTH levels in relation to serum corrected calcium (Source: www.parathyroid.com)

Patients in "Confusion Area B" have "normocalcaemic" primary hyperparathyroidism (NPHPT). This was first described in 2009. It is recognised as a variant of PHPT, which presents with high levels of PTH, but with normal serum-corrected calcium and ionised calcium levels. Some, but not all, patients will go on to develop PHPT. The diagnosis of NPHPT requires the exclusion of secondary causes of increased PTH, such as Vitamin D deficiency, renal insufficiency (estimated glomerular filtration rate <60 mL/min), malabsorption syndromes and medications such as diuretics, lithium, bisphosphonates, and denosumab.

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Approach to evaluation of PHPT

Table 3: Evaluation of patients with PHPT

Recommended
• Serum corrected (or ionised) calcium, PTH, phosphate, alkaline phosphatase, renal function tests, 25-hydroxy Vitamin D • 24 hour urine for calcium and creatinine excretion • Bone Mineral Density by DEXA (lumbar spine, hip, distal one-third radius) • Vertebral spine assessment (radiography, CT, or vertebral fracture assessment by DEXA) • Stone risk profile (if urine calcium excretion >100 mmol/ 24 hours) • Abdominal imaging by radiography, ultrasonography or CT scan
Optional Bone turnover markers e.g. osteocalcin and beta cross laps

- **Serum corrected calcium or ionised calcium:** Repeat measurements may be required as patients with PHPT can occasionally have temporarily normal calcium levels despite being hypercalcaemic most of the time. Patients with NPHPT have consistently normal serum corrected and ionised calcium levels.
- **Serum intact PTH:** Should be measured concomitantly with the serum calcium for evaluation. Low or undetectable PTH level rules out primary hyperparathyroidism and raises the possibility of cancer-associated hypercalcaemia, often mediated by PTH-related protein (PTH-rP), which does not cross-react with the PTH assay.
- **Urea and creatinine:** Should be done to assess renal function.
- **25-hydroxyvitamin D:** Levels below 20 ng/ml are common in PHPT, because PTH stimulates the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D.
- **Serum phosphate:** Levels are often decreased in PHPT due to the phosphaturic effect of PTH.
- **Alkaline phosphatase:** Helps in determining the extent of the bone disease. Elevated pre-operative levels predict post-operative hypocalcaemia following parathyroidectomy (Hungry Bone Syndrome).
- **24-hour urinary creatinine and calcium:** Quantifies urinary calcium excretion (often increased in nephrolithiasis) and explores the differential diagnosis of the rare familial hypocalciuric hypercalcaemia. A calcium:creatinine clearance ratio below 0.01 (fractional excretion of calcium <1%) suggests this diagnosis.
- **Genetic testing for MEN 1 and 2:** May be warranted in selected cases. Ampath offers testing for MEN 1 (menin gene) and MEN 2A (RET proto oncogene).

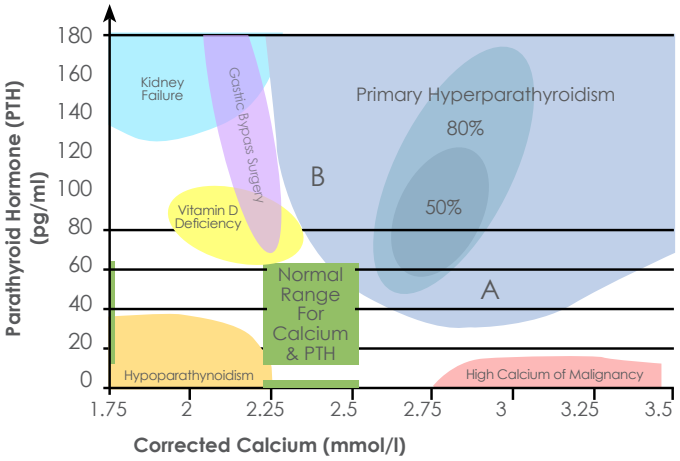

Figure 2: Other subsets that can cause confusion in the diagnosis of primary hyperparathyroidism (i.e other causes of hypercalcaemia or increased PTH) (Source: www.parathyroid.com)

Other considerations

1. Hypercalcaemia due to malignancy: Differs from classic PHPT in that the patients are generally severely ill, calcium values are usually markedly high (>3 mmol/l), resulting in a very low PTH.
2. Vitamin D deficiency: Low Vitamin D levels leads to reduced calcium absorption which in turn raises the PTH level.
3. Patients with severe chronic kidney disease (CKD) will develop secondary hyperparathyroidism due to hyperphosphataemia coupled with impaired renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which, in turn, causes hypocalcaemia. As a consequence, parathyroid chief cell hyperplasia occurs and PTH secretion increases. Tertiary hyperparathyroidism may develop because of prolonged hypocalcaemia that causes parathyroid gland hyperplasia. Autonomous oversecretion of PTH by the parathyroid glands results in hypercalcaemia.
4. Patients with intestinal malabsorption, such as gastric bypass surgery have difficulty absorbing calcium in their diet, thus hypocalcaemia stimulates secondary hyperparathyroidism.

References

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