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AMPATHCHAT

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Hypercalcaemia: A diagnostic approach

Hypercalcaemia is a relatively common clinical problem. Primary hyperparathyroidism and malignancy are the most common causes of hypercalcaemia, accounting for more than 90% of cases. The diagnostic approach to hypercalcaemia therefore involves distinguishing between these two main causes.

The definition of hypercalcaemia depends on the reference range of the laboratory and the precision of the analytical method. With a reference range of 2.15 to 2.50 mmol/l, a value in excess of 2.50 mmol/l should be considered as hypercalcaemia.

Calcium is corrected for the albumin level, as about 40% of calcium is bound to plasma proteins, of which 80% is bound to albumin. An ionized calcium level is also available, representing the biologically active calcium level, and should be considered whenever albumin- or acid-base disturbances are present.

Presentation of hypercalcaemia

Malignancy is often clinically evident by the time it causes hypercalcaemia, and patients with hypercalcaemia of malignancy usually have higher calcium concentrations and are more symptomatic from the hypercalcaemia (usually inpatients).

The most common presentation of hypercalcaemia is usually incidental detection on a biochemical screen. When symptoms are present, classically as "moans, bones, stones and groans", they include depressed mood, musculoskeletal pain, renal colic secondary to nephrolithiasis (kidney stones) and abdominal pain related to constipation or peptic ulcer disease.

Hypercalcaemia may be the cause of secondary hypertension, especially in patients younger than 35 years old. Patients may also present with polyuria and polydipsia secondary to the hypercalcaemia, causing an acquired form of nephrogenic diabetes insipidus. Renal involvement can also take the form of nephrocalcinosis and/or reduced renal function. Skeletal symptoms can take the form of pathological stress fractures, skeletal deformities and bone pain. As the severity of the hypercalcaemia progresses, nausea, vomiting, QT interval prolongation leading to cardiac arrest, delirium and coma may occur.

Table 1: Causes of hypercalcaemia

Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes type 1 and 2a
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcaemia (FHH)
Tertiary hyperparathyroidism (renal failure)
Non-parathyroid mediated
Hypercalcaemia of malignancy
PTHrP
Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Increased calcitriol (activation of extrarenal 1-alpha-hydroxylase)
Medications
Thiazide diuretics
Lithium
Recombinant PTH eg teriparatide
Excessive vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilisation
Parenteral nutrition
IV calcium infusion
Milk-alkali syndrome

Determining the cause

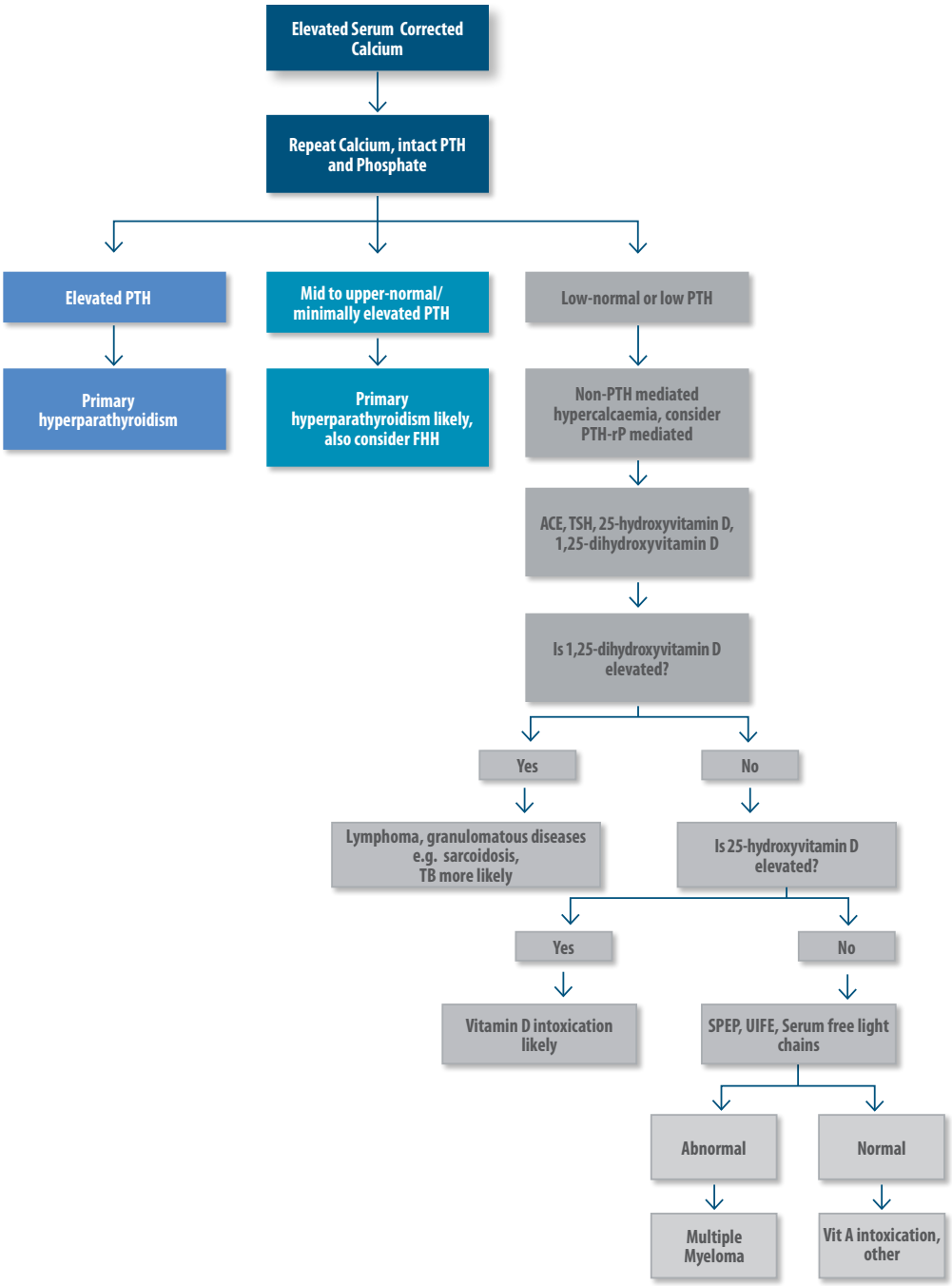
The aetiology may be obvious from the history and physical examination (Table 1). When the cause is not obvious or a suspected cause needs to be confirmed, other biochemical tests are indicated (Figure 1). If possible, any medication that may be causing hypercalcaemia should be discontinued. Thiazide diuretics may unmask and exacerbate a hypercalcaemia due to primary hyperparathyroidism, in which case stopping the diuretic is unlikely to reverse the hypercalcaemia.

Previous values for serum calcium should also be reviewed. The presence of longstanding asymptomatic hypercalcaemia is more suggestive of primary hyperparathyroidism, and also raises the possibility of familial hypocalciuric hypercalcaemia (FHH), a rare disorder of the calcium sensing receptor (CASR) causing hypercalcaemia. This condition usually presents in otherwise healthy outpatients and there may be a positive family history of hypercalcaemia.

The degree of hypercalcaemia is also useful diagnostically. Primary hyperparathyroidism is often associated with borderline or mild hypercalcaemia (serum calcium concentration, often below 2.75 mmol/L). Values above 3.25 mol/l are more common in patients with malignancy-associated hypercalcaemia.

Once hypercalcaemia is confirmed, the next step is the measurement of serum PTH as the initial goal of the lab evaluation is to differentiate PTH-mediated from non-PTH-mediated hypercalcaemia.

Figure 1: Evaluation of hypercalcaemia



- ***Elevated PTH:*** A frankly elevated PTH concentration in the setting of hypercalcaemia is likely the result of primary hyperparathyroidism. Primary hyperparathyroidism is due to hypersecretion of PTH. There is a female to male prevalence of 3:1. The cause is a solitary adenoma in 80% to 90% of cases. Chief cell hyperplasia is the cause in 20% of cases and carcinoma is rare (<2% of cases). Suspicion for parathyroid cancer should be increased when typically younger patients present with much higher serum calcium and PTH levels. Primary hyperparathyroidism can be part of the Multiple Endocrine Neoplasia (MEN) Syndrome types 1 and 2a. The majority of patients are asymptomatic and are identified on screening, however, some patients have overt bone disease e.g. osteitis fibrosa cystica, but may also present with nephrocalcinosis, nephrolithiasis or pancreatitis.
- ***Mid to upper-normal or minimally elevated PTH:*** 10% to 20% of patients with primary hyperparathyroidism have a serum PTH in the upper end of the normal range; such a "normal" level is inappropriately high in the presence of hypercalcaemia. Hence the diagnosis of primary hyperparathyroidism should be considered. The diagnosis of FHH should also be considered and 24-hour urinary calcium should be measured to distinguish it from primary hyperparathyroidism. Alternatively the urine calcium excretion and calcium/creatinine clearance ratio may be calculated using a fasting serum and timed urine sample. In FHH, virtually all patients will have hypercalcaemia by age 30 years. Two other clues to the diagnosis of FHH are a family history of hypercalcaemia (autosomal dominant) and few, if any, symptoms of hypercalcaemia. The 24-hour or fasting urinary calcium excretion will be very low (fractional excretion of calcium <1%) in FHH. However, low urinary calcium excretion can also be compatible with primary hyperparathyroidism because of the calcium conserving renal actions of PTH, and dietary calcium intake is low. Genetic testing for mutations in the calcium sensing receptor is unfortunately not locally available.
- ***Low PTH:*** A low or low-normal serum intact PTH level (below 20 pg/ml) is consistent with non-PTH mediated hypercalcaemia. In the presence of hypercalcaemia and low serum PTH, Vitamin D metabolites and other lab tests, e.g. serum protein electrophoresis (SPEP) and TSH, should be performed to elucidate the diagnosis, depending on history and clinical features.
- ***PTH-related protein (PTH-rP):*** Humoral hypercalcaemia of malignancy is a common cause of non-PTH-mediated hypercalcaemia. It should be suspected if the hypercalcaemia is of relatively recent onset and there is clinical evidence of malignancy, usually from a solid tumour. Most tumours causing hypercalcaemia are large and easily recognised with notable neuroendocrine exceptions, e.g. phaeochromocytomas and islet cell tumours. Hyperparathyroidism and humoral hypercalcaemia of malignancy due to high PTH-related peptide may be associated with hypophosphataemia due to the phosphaturic action of PTH. PTH-related peptide level is usually inferred from a low intact PTH level (at least a second generation assay, which is specific for PTH and does not cross react with PTH-related peptide). Measurement of PTH-rP is not routinely available. 1,25 $(OH)_2$-Vitamin D is low in a PTH-rP-mediated hypercalcaemia, whereas it is high in PTH-mediated hypercalcaemia because PTH increases activation of 25 (OH)-Vitamin D to 1,25 $(OH)_2$-Vitamin D, which is the active form.
- ***Vitamin D Metabolites:*** In primary hyperparathyroidism, a decrease in 25-hydroxyvitamin is more likely because PTH stimulates the conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D. Although this might seem paradoxical, namely that Vitamin D deficiency is a possible clinical problem when the 25-hydroxyvitamin D level is low and active 1,25 dihydroxyvitamin D is normal or high, it may be the case warranting treatment with 25-hydroxyvitamin D. An elevated serum concentration of 25 (OH)-vitamin D is indicative of Vitamin D intoxication due to the ingestion of either form of 25 (OH)-Vitamin D, cholecalciferol or calcidiol. Increased levels of 1,25 $(OH)_2$-Vitamin D may be induced by direct intake of calcitriol, extra renal production in granulomatous diseases/ lymphoma or increased renal production induced by primary hyperparathyroidism.

Laboratory evaluation of hypercalcaemia

The following investigations are recommended: PTH, serum phosphate, Creatinine with eGFR, 25(OH)D,1,25 $(OH)_2D$, 24-hour urinary calcium or hypocalciuria profile. Table 2 shows the laboratory findings that can assist in confirming specific causes of hypercalcaemia.

Additional laboratory evaluations to consider if diagnosis is still uncertain: Serum Protein Electrophoresis (SPEP), Urine Protein Electrophoresis (UPEP), Serum-free light chains, Serum and urine immunofixation (IFE) and Vitamin A levels.

Table 2: Laboratory findings for specific aetiologies of hypercalcaemia

Aetiology	PTH	PTHrP	1,25 $(OH)_2D$	25(OH)D	Phosphate
PTHrP mediated	Low	High	Low or normal	Any value	Low
1,25 $(OH)_2D$ mediated	Low	Low	High	Low or normal	Low
PTH mediated	High	Low	High	Low or normal	Low
Vitamin D intoxication	Low	Low	High	High	Normal/ high

Other tests: In the absence of malignancy or increased PTH-rP, unsuspected stimulation of bone resorption (as with multiple myeloma, thyrotoxicosis, immobilization or vitamin A toxicity) and unrecognised calcium intake are the most likely causes to consider. A 24-hour urinary calcium test is recommended to assist in differentiating between FHH and PHPT, or to profile risk for urinary stones if hypercalciuria is present. There are a few conditions in which there is a relative hypocalciuria (less than 100 mg/day or <2.5 mmol/day) including the use of thiazide diuretics (increased calcium resorption in the distal convoluted tubule) and FHH, in which the fractional excretion of calcium is <1%. Fasting urine calcium excretion is the best single parameter to differentiate familial benign hypercalcaemia from primary hyperparathyroidism. When the level of PTH is inappropriately elevated for the serum calcium, that is a PTH level of between 25 and 65 pg/mL in the face of hypercalcaemia, it is necessary to collect fasting urine and blood samples to measure fasting urine calcium excretion (so-called "Hypocalciuria profile").

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