Hypercalcaemia and primary hyperparathyroidism

Jeremy J O Turner

Abstract

Hypercalcaemia is most commonly caused by primary hyperparathyroidism (PHPT) or malignancy. PHPT is common, affects women more than men, and is usually caused by a solitary parathyroid adenoma. The most common presentation is an asymptomatic incidental finding on blood tests performed for another indication. The only curative treatment is parathyroidectomy. In 2014, the Fourth International Workshop on the management of asymptomatic PHPT updated its guidance on the management of asymptomatic PHPT. It recommended surgery in: all symptomatic patients; asymptomatic patients with hypercalcaemia >0.25 mmol/litre above the upper limit of the reference range, evidence of end-organ damage, including impaired renal function, reduced bone mineral density, established vertebral fractures and hypercalciuria; and patients <50 years old. In other patients with PHPT, conservative management with regular monitoring is an acceptable management strategy. Defining 'asymptomatic' is not always easy, and there is growing awareness of the prevalence of reduced quality-of-life scores among patients with 'asymptomatic' PHPT; however, there is a lack of definitive evidence showing benefit in these domains following parathyroidectomy. Therefore, careful clinical decision-making is required in this group of patients.

Keywords Cinacalcet; hypercalcaemia; parathyroidectomy; primary hyperparathyroidism; vitamin D

Key points

- The Fourth International Workshop on asymptomatic primary hyperparathyroidism (PHPT) has released updated guidance on the management of asymptomatic PHPT
- The Society for Endocrinology has recently published guidance on the emergency management of severe hypercalcaemia
- The novel anti-resorptive denosumab is increasingly seen as having a role in management of severe hypercalcaemia (although this is currently an unlicensed indication in the UK)
- Preoperative imaging in primary hyperparathyroidism is increasingly moving towards SPECT-CT scanning and away from ultrasonography + planar MIBI scanning
- Mutations in an increasing number of genes are now recognized in the aetiology of familial PHPT syndromes

Aetiology

Of the numerous causes of hypercalcaemia, primary hyperparathyroidism (PHPT) is the most common in outpatient settings, and malignancy is most common among inpatients. PHPT is characterized by hypercalcaemia with elevated or inappropriately 'normal' concentrations of parathyroid hormone (PTH) and elevated urinary calcium excretion. The prevalence is 1–3/1000. It is more common in women (3:1) and usually presents after the age of 50 years.

The main causes of PHPT are outlined in Table 1. PHPT is usually sporadic, but can be familial and associated with a number of genetic abnormalities, as summarized in Table 2. These inherited forms tend to present at a younger age. Guidelines for the management of PHPT and other clinical features in multiple endocrine neoplasia type 1 (MEN-1) have recently been published.

Jeremy J O Turner *DPhil FRCP is a Consultant Endocrinologist at the Norfolk and Norwich University Hospitals, Norwich, UK. Competing interests: none declared.*

Clinical features

Patients are commonly asymptomatic at diagnosis, with serum calcium <0.25 mmol/litre above the reference range. Classical symptoms include polyuria, polydipsia, depression, peptic ulcer disease, musculoskeletal aches and pains and renal colic ('moans, bones, stones and groans'). Some reports have linked asymptomatic PHPT to reduced quality-of-life scores, but this does not consistently improve after parathyroidectomy.[1,2] Similarly, although an association has been described between PHPT and hypertension, it has not been shown to consistently improve following parathyroidectomy. Features of end-organ damage include osteoporosis, osteitis fibrosa cystica, nephrolithiasis and nephrocalcinosis. Classical skeletal changes (brown tumours, osteitis fibrosa cystica) occur in <2% of patients with PHPT, but osteoporosis is a common feature of hyperparathyroidism and predominantly affects cortical bone (e.g. distal radius) rather than trabecular bone (e.g. vertebral bodies).

Diagnosis and investigations

Elevated or inappropriately 'normal' plasma PTH concentration with elevated serum calcium (adjusted for serum albumin) is almost diagnostic of PHPT (Figure 1).

The exception to this is familial hypocalciuric hypercalcaemia (FHH), which can mimic the serum biochemistry of PHPT and is

Aetiology of PHPT

Cause	Proportion of PHPT cases
Single parathyroid adenoma	80–85%
Multiple parathyroid adenomas, four-gland hyperplasia	15–20%
Parathyroid carcinoma	<0.5%

Table 1

Please cite this article in press as: Turner Jeremy J O, Hypercalcaemia and primary hyperparathyroidism, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.06.010

Genes associated with heritable PHPT syndromes

Disorder	Gene
MEN1	*MEN1*
MEN2	*RET*
MEN4	*CDKN1B*
HPT-JT	*CDC73*
FIHPT	*MEN1*, *CDC73*, *CASR*, *CDKN1A*, *CDKN2B*, *CDKN2C*
NSPHPT	*CASR*
nsPHPT	*PTH*

FIHPT, familial isolated hyperparathyroidism; HPT-JT, hyperparathyroidism jaw tumour syndrome; NSPHPT, neonatal severe PHPT; nsPHPT, non-syndromic PHPT.

Table 2

distinguishable only by urine biochemistry. FHH is an autosomal dominant condition usually caused by inactivating mutations in the calcium-sensing receptor gene (CASR), although it has more recently also been linked to mutations of the *AP2S1* and *GNA11* genes. It is characterized by a modest increase in serum calcium with an inappropriately normal plasma PTH (slight elevation in 5−10% of patients). The calcium:creatinine clearance ratio is used to distinguish PHPT from FHH. This ratio is calculated from simultaneous measurements of urine and serum calcium and creatinine concentrations. A value of <0.01 is indicative of FHH.

The interaction of PHPT with vitamin D deficiency has received much attention. Vitamin D deficiency can mask hypercalcaemic PHPT and can drive the hyperparathyroid state, increasing skeletal disease activity in PHPT. An assessment of vitamin D status should therefore be performed whenever calcium or PTH biochemistry is abnormal.

Elevated PTH with normal calcium, so-called normocalcaemic hyperparathyroidism, is an increasingly common biochemical finding. It is diagnosed by excluding causes of secondary hyperparathyroidism, such as vitamin D deficiency and renal disease, and may represent 'early' PHPT before serum calcium has had time to rise.[3] However, its natural history is not well described.

Management

Surgery is the only curative treatment for PHPT but is not appropriate in all patients; the potential benefits must be weighed against the risks in each case. This process has been simplified by the publication of guidelines from the Fourth International Workshop on the management of asymptomatic PHPT (Table 3).[4] However, these guidelines do not apply in the familial PHPT syndromes described above.

Surgery

Surgery is indicated in all symptomatic patients and asymptomatic patients with evidence of end-organ damage, specifically:

- impaired renal function

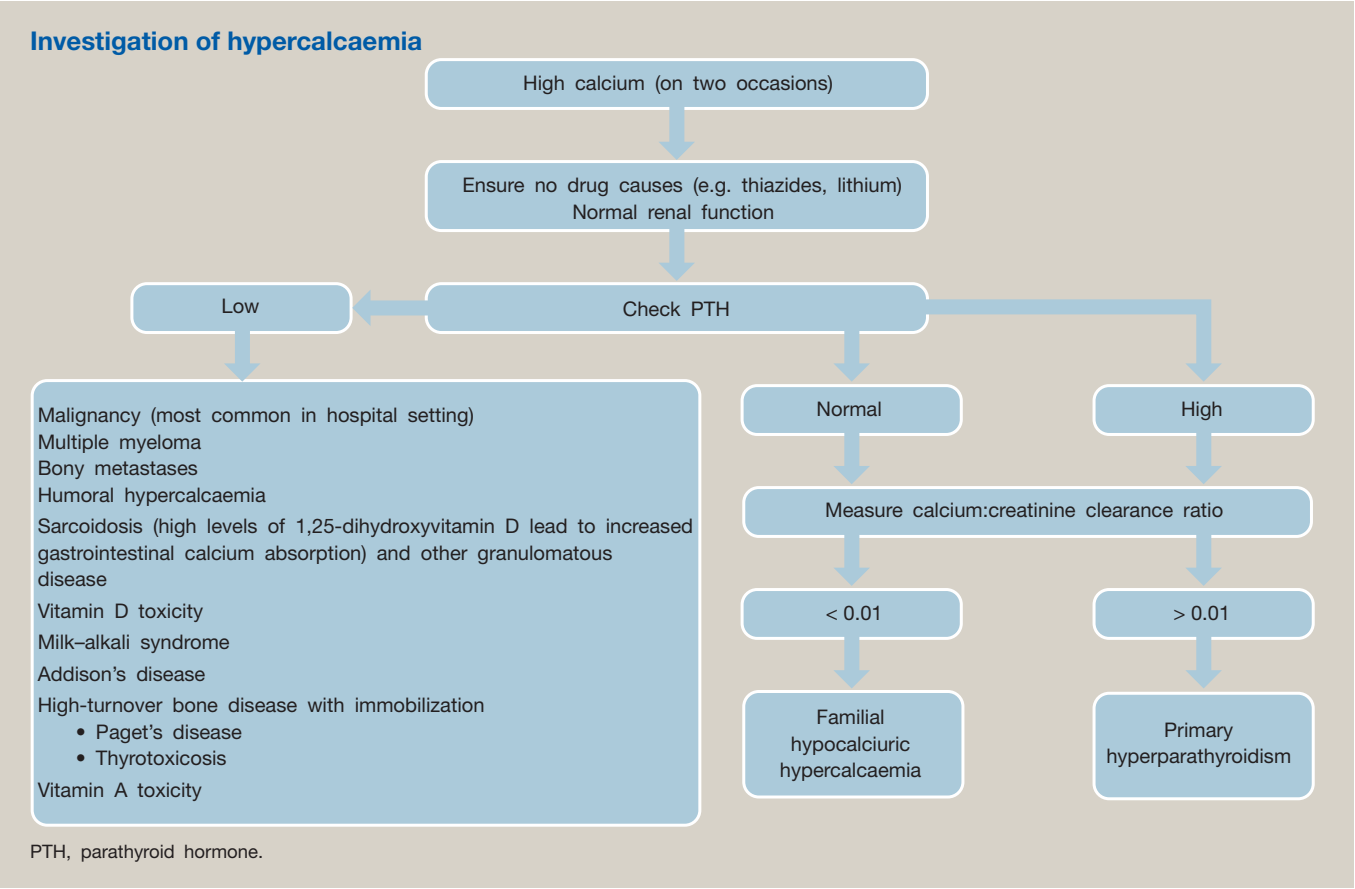

Figure 1

Please cite this article in press as: Turner Jeremy J O, Hypercalcaemia and primary hyperparathyroidism, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.06.010