Disappearing hypercalcaemia

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Summary: Four women presented with symptomatic hypercalcaemia and raised concentrations of serum parathyroid hormone (PTH). In each case, serum calcium returned spontaneously to normal. In two patients serum PTH also fell to the normal range and biochemical relapse has not occurred despite prolonged follow-up. In the others, serum PTH remained elevated and subsequent symptomatic hypercalcaemia necessitated parathyroidectomy. In the first two cases, autoperathyroidectomy is the most likely explanation; the initial fall in serum calcium in the other two patients is unexplained. Large fluctuations in serum calcium may occur in some patients with hyperparathyroidism and prolonged and careful observation is required when this occurs.

Introduction

Hyperparathyroidism is characterized by hypercalcaemia in association with elevated levels of serum parathyroid hormone (PTH).¹ Minor fluctuations in serum calcium may occur in this condition. However, we report four patients with significant hypercalcaemia (serum calcium > 2.97 mmol/l) and elevated PTH concentrations, in whom serum calcium returned to normal without specific treatment.

Case reports

Case 1

An 82 year old woman presented with a 3-week history of confusion, constipation and nausea. She became immobile 2 days before hospital admission. There was no history of self-medication with vitamin D or antacids and no significant past medical history. On examination, she was found to be dehydrated and drowsy with corneal calcification. Plasma concentrations were as follows: urea 11.6 mmol/l (normal 2.5–6.5), creatinine 192 µmol/l (60–120), sodium 145 mmol/l (136–48), chloride 99 mmol/l (95–105), potassium 3.9 mmol/l (3.7–5.4), total CO₂ 24 mmol/l (22–27), free thyroxine 19 pmol/l (9–23), inorganic phosphate 0.85 mmol/l (0.8–1.4), alkaline phosphatase 83 IU/l (21–92) and serum calcium was > 4.01 mmol/l (2.1–2.6) on three occasions with serum albumin 44 g/l. The haemoglobin concentration was

16.9 g/dl (12–16), the appearance of the blood film was normal and the erythrocyte sedimentation rate (ESR) was 4 mm/hour. Skeletal survey and technetium-99 bone scan showed no evidence of bone disease and a chest X-ray was normal.

She was treated with intravenous 0.9% saline, frusemide and oral prednisolone (40 mg/day). Over the next few days, her condition improved markedly and serum calcium gradually returned to the normal range. However, PTH estimation on blood taken at the time of admission was subsequently found to be 470 pg/ml (normal range <120, N-terminal assay) indicating hyperparathyroidism. Convalescence was complicated by an attack of acute pancreatitis and she was discharged from hospital 8 weeks after admission. Serum calcium remained within the normal range despite withdrawal of prednisolone 3 weeks after admission and she remains normocalcaemic (serum calcium 2.46 mmol/l) and asymptomatic 18 months later. Plasma PTH estimations on two occasions following discharge from hospital have been <40 pg/ml.

Case 2

A 55 year old woman presented to her general practitioner with a 4-week history of lethargy, anorexia and backache. There was no medical history of note and no history of self-medication with antacids or vitamin preparations. Examination revealed no abnormality but serum calcium was 3.97 mmol/l and inorganic phosphate 1.51 mmol/l. She was referred to the medical outpatient department where she was seen 6 weeks later. At that time serum calcium was high

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Accepted: 13 March 1987

normal (2.50 mmol/l) and her symptoms had completely resolved. Other investigations were as follows: urea 5.6 mmol/l, creatinine 107 μ mol/l, sodium 143 mmol/l, potassium 4.9 mmol/l, total CO₂ 25 mmol/l, inorganic phosphate 1.11 mmol/l, serum albumin 44 g/l, and serum PTH was 300 pg/ml (normal range <120, N-terminal assay). Haemoglobin concentration was 12.3 g/dl, ESR 10 mm/hour and serum immunoglobulin concentrations normal. X-rays of the chest and hands and a skeletal survey showed no abnormality. She has been followed up for 2 years and serum calcium has remained normal. Serum PTH has now fallen to <40 pg/ml on two occasions.

Case 3

A 72 year old woman presented to her family practitioner with a 6-month history of weight loss, constipation, polyuria, polydipsia and lethargy. She was taking no medication and past medical history was unremarkable. There were no significant findings on examination but serum calcium was 4.01 mmol/l. She was referred to the medical outpatient department where hypercalcaemia was confirmed (4.02 mmol/l) and further investigation revealed that the plasma urea was 4.9 mmol/l, creatinine 69 μ mol/l, sodium 144 mmol/l, potassium 4.3 mmol/l, total CO₂ 25 mmol/l, inorganic phosphate 0.56 mmol/l, serum albumin 45 g/l and alkaline phosphatase 1080 IU/l. Haemoglobin concentration was 15.3 g/dl, ESR 29 mm/hour and a discrete band was noted in the gamma region on serum

electrophoresis; serum immunoglobulin concentrations, however, were normal. X-rays of the pelvis, spine, skull and femora were normal but X-ray of the hands revealed subperiosteal resorption of bone.

On review 4 weeks later, she was feeling very much better and the serum calcium was normal on this occasion (2.38 mmol/l) although serum PTH was elevated, being 4.25 ng/ml (normal range <0.2, C-terminal assay) (Figure 1). Serum 25-OH vitamin D concentration was measured and was normal. She remained normocalcaemic for the next 5 months with an elevated PTH concentration but was then admitted to hospital with confusion, polyuria, slurred speech and abdominal pain. Serum calcium was once more found to be raised (4.3 mmol/l), inorganic phosphate was 0.73 mmol/l and alkaline phosphatase 259 IU/l. She was treated with intravenous infusion of 0.9% saline, calcitonin (400 U q.d.s. intramuscularly) and oral phosphate supplements.

Her symptoms resolved as the serum calcium returned to normal, at which time she underwent surgical exploration of the neck. A nodule measuring 12 $\times$ 5 $\times$ 2 mm was removed from the right side of the neck and histological examination revealed the typical changes of a parathyroid adenoma with clear chief cells arranged in cords and alveolar groups. Other specimens from the left side of the neck comprised normal parathyroid tissue. Postoperatively, the patient developed symptomatic hypocalcaemia (serum calcium 1.5 mmol/l) and required oral and intravenous calcium supplements as well as 1-alpha-

Figure 1 Serum calcium and parathyroid hormone concentrations in case 3 showing temporary remission of hypercalcaemia.

hydroxycholecalciferol to maintain serum calcium within the normal range. Over the next 4 months, these drugs were withdrawn and she remains well and normocalcaemic 3 years later.

Case 4

A 72 year old woman was admitted with a 6-week history of lethargy, weakness and weight loss. She had suffered from asthma for many years (controlled by inhaled steroids and bronchodilators and oral prednisolone) and was also taking thyroxine 150 µg/day following radio-iodine treatment 30 years previously for thyrotoxicosis.

Mild hypercalcaemia (serum calcium 2.7 mmol/l) had been discovered by routine biochemical analysis 13 years previously and this persisted for the next 10 years. On two occasions serum PTH concentration was estimated and found to be greater than 0.76 ng/ml (normal range <0.2 C-terminal assay). No radiological features of hyperparathyroidism were present. During the 3 years prior to admission, the patient's serum calcium had fallen to 2.42 mmol/l but the serum PTH concentration was consistently elevated, varying between 0.8 and 1.3 ng/ml.

Examination revealed rhonchi on auscultation of the chest and proximal muscle weakness. Serum calcium concentration was again elevated at 2.97 mmol/l and serum PTH was 1.2 ng/ml. Plasma urea was 6 mmol/l, creatinine 99 µmol/l, sodium 141 mmol/l, potassium 4.4 mmol/l, serum albumin 42 g/l, alkaline phosphatase 174 U/l (70–350), haemoglobin 11.5 g/dl and ESR 5 mm/h. At surgical exploration of the neck, a large (1.5 cm diameter) adenoma was removed from the right upper pole of the thyroid gland. Histological examination confirmed that this was an adenoma of the parathyroid. Transient hypocalcaemia developed post-operatively and the patient remains well and normocalcaemic 2 years later.

Discussion

All our patients were females aged over 55 years and they presented with symptoms directly attributable to hypercalcaemia which resolved when serum calcium concentrations returned to the normal range. In all four, hypercalcaemia was accompanied by significant elevation of serum PTH concentration suggesting hyperparathyroidism.¹ The remarkable feature is that in each case, serum calcium returned to the normal range without specific treatment.

Two different biochemical patterns were observed. In the first two cases, serum PTH and calcium concentrations fell to the normal range at about the

same time suggesting spontaneous remission of hyperparathyroidism. In the third and fourth cases, however, PTH levels remained elevated in spite of a fall in serum calcium to normal and subsequent relapse of hypercalcaemia necessitated parathyroidectomy in both instances.

A number of explanations might be offered for these observations. Firstly, there may have been another cause for hypercalcaemia but careful investigation in each case failed to confirm this possibility. The other main cause of hypercalcaemia, non-parathyroid malignancy,² is very unlikely as the patients all remain well after follow-up periods of 18 months to 4 years. The high plasma phosphorus with normal renal function in case 2 would be unusual in hyperparathyroidism but PTH concentration was considerably elevated and alternative diagnoses seem improbable.

Assuming, then, that the hypercalcaemia was due to hyperparathyroidism, what explanation may be offered for the marked fluctuation in serum calcium levels? In early and mild cases of hyperparathyroidism, it is possible for serum calcium levels to fluctuate so as sometimes to lie within the normal range.³ However, the fluctuations are usually relatively minor, and occur around the upper limit of the normal range and not from normocalcaemia to gross hypercalcaemia as described in cases 1–3. Similar biochemical findings may be seen in some patients with renal calculi and hypercalciuria in whom renal loss of calcium leads to secondary hyperparathyroidism. Once again, normocalcaemia is associated with elevated PTH concentrations but gross hypercalcaemia does not occur.^{4,5}

Associated vitamin D deficiency may also lead to normocalcaemic hyperparathyroidism;⁶ in one of our cases the alkaline phosphatase concentration was markedly elevated but serum 25-OH vitamin D was normal and there was no radiological evidence of osteomalacia. The alkaline phosphatase concentration gradually fell only to rise again during relapse of hypercalcaemia; a sustained fall in concentration followed parathyroidectomy suggesting the underlying cause was the hyperparathyroid state. There was no evidence of vitamin D deficiency in the other three cases. Finally, hypoalbuminaemia and acidosis may cause normocalcaemia but are not relevant in these cases.

An alternative suggestion is that two patients (cases 1 and 2) underwent 'autoparathyroidectomy'. This is extremely rare but has been described in one patient with a parathyroid carcinoma⁷ and another with a parathyroid adenoma⁸ and may be due to the tumour outstripping its blood supply. Another possibility is that, in rare instances, the parathyroid may become temporarily overactive causing a 'parathyroid storm', a situation analogous to the hyperthyroidism accompanying thyroiditis.

The situation is further complicated by the fact that in cases 2, 3 and 4, serum calcium concentrations returned to normal at a time when PTH concentrations were still elevated. This might be explained by secretion of an immunologically reactive PTH molecule with decreased biochemical potency or alteration in hormone receptor number or availability. This disparity has been observed in pseudohypoparathyroidism and in vitamin D deficiency where immunoreactive PTH can remain elevated in the presence of normal levels of bioactive PTH and normocalcaemia⁹ and familial hypocalciuric hypercalcaemia where bioactive PTH is in the normal range and immunoreactive PTH may be undetectable.¹⁰ However, such an explanation would require sudden switching of PTH production to a form with low

biological potency and this seems unlikely to occur.

These cases demonstrate that serum calcium in some patients with hyperparathyroidism may show marked fluctuation from toxic levels to the normal range. Unexpected and dramatic biochemical relapse may occur so that prolonged and careful review is necessary. We suggest that all patients with fluctuating hypercalcaemia are followed up at regular intervals until the pathogenesis and course becomes clearer.

Acknowledgements

We would like to thank Professor J.L.H. O'Riordan for arranging some of the parathyroid hormone assays and for helpful advice.

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