Life-threatening hypercalcaemia in association with Addisonian crisis

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Summary: A 35 year old woman was admitted with acute radial artery occlusion necessitating two operations and thrombolytic therapy. Subsequently a diagnosis of primary hypothyroidism was made and she was commenced on thyroxine replacement therapy. Her condition, however, continued to deteriorate with the development of an Addisonian crisis heralded by, and complicated by, severe, life-threatening hypercalcaemia. This case highlights the importance of considering Addison's disease in any patient whose condition deteriorates after the introduction of thyroxine replacement, and illustrates the often forgotten association of hypercalcaemia and hypoadrenalism.

Introduction

Hypercalcaemia in association with hypoadrenalism was first described in 1932¹ and although well recognized since, its true prevalence probably remains underestimated.

Life-threatening hypercalcaemia, however, is rare, and, in the published cases, has tended to occur in patients with associated parathyroid disease; either treated hypoparathyroidism^{2,3} or coexistent hyperparathyroidism.⁴ We report a case of life-threatening hypercalcaemia heralding Addisonian crisis in a young female patient, who had recently been commenced on thyroxine replacement therapy following the diagnosis of primary hyperthyroidism.

Case report

A 35 year old Caucasian female presented with acute radial artery occlusion. She had been previously well, though had been investigated for infertility some 5 years previously. She gave a strong family history of myocardial infarction in youth, and her mother had undergone thyroidectomy for Graves' disease. Despite operative intervention on two occasions and subsequent thrombolytic therapy combined with systemic anticoagulation she developed gangrene of the left hand. Post-operative recovery was further complicated by the development of non-specific chest

pain, repeated hypotensive episodes, nausea and vomiting. Investigation revealed the following results: anaemia (Hb 9.6 g/dl), macrocytosis (107 fl) and eosinophilia (0.3%), normal B12 (499 ng/l, normal range: 180–800 ng/l) and serum folate (2.4 µg/l; normal range 1.6–10 µg/l), an elevated ESR at 81 mm/h; moderately impaired renal function (creatinine 174 mmol/l) and hyperphosphataemia (2.23 mmol/l); normal chest X-ray and lung scan, fatty liver infiltration on ultrasound; elevated thyroid stimulating hormone (TSH) (61 mU/l), strongly positive thyroid microsomal antibodies (1:102,400), and elevated prolactin (2,200 mU/l). A diagnosis of primary hypothyroidism was made and she was commenced on thyroxine 100 µg/day. Over the next 25 days her condition continued to deteriorate with the development of hyponatraemia, hyperkalaemia and hypercalcaemia. Serial calcium measurements (corrected for albumin) are illustrated graphically in Figure 1.

At the time of her peak corrected calcium (3.92 mmol/l), a single 09.00 h cortisol measurement was 60 nmol/l, and she was referred to the endocrine team. She was clearly unwell, hypotensive and dehydrated with pigmentation over her knuckles, elbows and in the recent operation scar. She was hyponatraemic (122 mmol/l) and hyperkalaemic (5.3 mmol/l). A short Synacthen test confirmed the diagnosis of Addison's disease; cortisols at 0, 30 and 60 minutes were <60, <60 and <60 nmol/l, respectively, with a basal ACTH concentration of 698 ng/l (normal range: 10–80). Adrenal antibodies on this, and two subsequent occasions, were negative. She was vigorously rehydrated and commenced on hydrocortisone

Figure 1 Variation in serum calcium concentrations (corrected for albumin) prior to and directly after commencement of hydrocortisone. The shaded area represents the normal range of our laboratory (T4 = thyroxine).

100 mg 6 hourly intramuscularly, resulting in a rapid symptomatic improvement and resolution of the electrolyte abnormalities within 48 hours. Levels of intact parathyroid hormone were undetectable prior to and 24 hours after the introduction of hydrocortisone; serial measurements of magnesium and vitamin D were consistently within the lower end of the normal laboratory range. She subsequently made an uneventful recovery and at review 3 weeks later her prolactin had returned to normal (370 mU/l). Computerized tomography (CT) showed small adrenal glands.

No cause for her radial artery occlusion was established; her clotting screens were normal, estimations of protein C, protein S and antithrombin 3 concentrations were within the normal range, anti-cardiolipin antibodies were negative, and echocardiography revealed no source of embolus.

Discussion

Our patient had primary hypothyroidism and Addison's disease heralded by hypercalcaemia. Despite the negative adrenal antibodies it is likely that the Addison's disease was autoimmune in origin as she had small adrenals on her CT scan and strongly positive thyroid antibodies. Adrenal antibodies are not always found in Type II polyglandular autoimmune disease.

Early reviews in man⁵⁻⁹ and adrenalectomized dogs⁵ suggest that the incidence of hypercalcaemia in hypoadrenalism is approximately equivalent to that of hyponatraemia, although there would appear to be no direct correlation between the two parameters in the same subjects.

The mechanisms involved in the development of

hypercalcaemia in Addison's disease are not fully understood, but would appear to be independent of changes in parathyroid hormone and vitamin D concentrations. Indeed, the raised phosphate estimations and undetectable parathyroid hormone levels in our patient are against any abnormality in parathyroid hormone secretion. There are three remaining possible mechanisms: increased calcium absorption from the gut, increased calcium absorption from bone and decreased renal excretion of calcium.

Walser and colleagues⁵ studied the effects of adrenalectomy on mongrel dogs. Animals fed a calcium- and magnesium-free diet demonstrated the same incidence and degree of hypercalcaemia as those fed a normal diet, suggesting that increased calcium absorption from the gut would not appear to be an important factor in the development of hypercalcaemia.

Jowsey and Simons¹⁰ investigated the contribution of increased bone resorption of calcium, particularly with respect to the associated effects of thyroxine. Mongrel dogs were divided into three groups, each group undergoing either thyroidectomy, thyroparathyroidectomy or parathyroidectomy. Following the neck surgery, animals were subjected to adrenalectomy and were treated with prednisolone until post-operative recovery was complete. Parathyroidectomized animals showed precipitous increases in calcium levels, despite being maintained on a calcium- and magnesium-free diet. Thyroidectomized animals, on the other hand, showed no significant increases in calcium until thyroxine replacement therapy was commenced when there was a rapid rise in calcium concentrations; a situation analogous to that of our patient. It was concluded that hypoadrenal hypercalcaemia was due to increases in calcium resorption from bone, mediated by thyroxine.

A third possible mechanism involves the reduction in glomerular filtration rate occurring as a result of hypovolaemia, which in turn results in an increase in proximal tubular reabsorption of sodium with concurrent calcium reabsorption. In a well studied case, a patient with idiopathic hypoparathyroidism treated with vitamin D and calcium supplements developed Addison's disease associated with severe hypercalcaemia.² Serial assessments of urinary sodium and calcium excretion were made when the patient was both on and off cortisone treatment. Cortisone replacement resulted in calciuresis with increased creatinine clearance, whereas withdrawal of cortisone (due to recurrent hypocalcaemia) led to natriuresis without calciuresis. These results, taken in conjunction with the observation of hypercalciuria in Cushing's disease and the fact that fluid replacement alone cannot reverse the hypercalcaemia of Addison's disease, suggest that an adequate circulating level

of corticosteroid is a prerequisite for the unimpaired excretion of calcium.

In summary, hypercalcaemia in Addison's disease is not uncommon, although life-threatening levels are rarely attained. In this case it seems highly likely that the hypercalcaemia was due to adrenal insufficiency as other causes of steroid responsive hypercalcaemia had been excluded by detailed investigation. The aetiology of hypoadrenal hypercalcaemia would appear to be multifactorial with alterations in the resorption of calcium from bone and its urinary excretion. In this case, it seems highly likely that the introduction of thyroxine therapy had the dual effect of unmasking Addison's disease and contributing to the associated hypercalcaemia. Indeed, Addison's disease

should be suspected in any such patient who shows a deterioration in symptoms following the introduction of thyroid replacement. Furthermore, abnormal thyroid function tests are often seen in relation to Addison's disease, the biochemical abnormalities returning to normal on hydrocortisone replacement therapy. In this case, however, the presence of thyroid microsomal antibodies in high titres suggested an underlying diagnosis of primary hypothyroidism.

It is important for clinicians to remember the association between hypoadrenalism and hypercalcaemia, as the electrolyte abnormalities are rapidly reversed with the combination of adequate fluid replacement and hydrocortisone therapy.

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Erratum

"Life-threatening hypercalcaemia in association with Addisonian crisis". *Postgraduate Medical Journal* 1991 67: 770–772.

The authors for this paper should have read as

follows: John Miell¹, Wassif Wassif², Alan McGregor¹, Joan Butler² and Richard Ross¹. Dr Wassif's name was unfortunately omitted from the list of authors.

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