Case report

Secondary hypoadrenalism presenting with hypercalcaemia

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Summary

We describe a young woman with lymphocytic hypophysitis presenting in the early post-partum period. She had selective corticotroph failure causing secondary adrenal insufficiency. At the time of presentation she had transient hyperthyroidism due to thyroiditis, and hypercalcaemia. This is the third case to be described of hypercalcaemia occurring in association with lymphocytic hypophysitis. Hypercalcaemia is not a recognized complication of other forms of pituitary failure. The two previously described cases also had selective corticotroph failure and hyperthyroidism due to thyroiditis. This pattern of presentation supports the concept that thyroid hormone action in the presence of glucocorticoid deficiency is responsible for the increased calcium efflux from bone into the circulation. Reduced renal excretion of calcium due to a reduction in calcium delivery to the glomerulus and increased proximal tubular reabsorption are also implicated in the aetiology of hypercalcaemia associated with adrenal failure.

Hypercalcaemia is a recognized complication of Addison's disease. Two major mechanisms which are not mutually exclusive have been invoked to explain the aetiology of this condition in primary adrenal failure. These are, firstly, a reduction in calcium excretion by the kidneys and, secondly, an increase in calcium release from bone (Miell et al., 1991). Increased calcium absorption from the gut has been discounted as a possible factor (Walser et al., 1963), as has an increased activity of the parathyroid (PTH)-1,25(OH)2D axis (Walker & Davies, 1981; Muls et al., 1982). We describe a patient with hypoadrenalism secondary to pituitary corticotroph failure due to lymphocytic hypophysitis who presented with hypercalcaemia which responded to glucocorticoid replacement therapy. This unusual presentation, which has previously been described in two cases in the literature, provides additional insights into the aetiology of hypercalcaemia of adrenal failure.

Case history

A 29-year-old previously healthy woman presented 10 weeks after normal delivery of her third child with marked fatigue, generalized weakness, weight loss, vomiting and failed lactation. She had noticed increasing fatigue and lethargy during the third trimester of pregnancy. She had developed facial and peripheral oedema at 36 weeks' gestation and her blood pressure was 150/90 mmHg at 39 weeks but there was no proteinuria and she was managed conservatively. She delivered a healthy baby with no peripartum haemorrhage or hypotensive episode. The fatigue and generalized weakness worsened post partum accompanied by myalgia, arthralgia, nausea and vomiting. She failed to lactate and was amenorrhoeic at the time of presentation. She noted weight loss of approximately 30 kg in the 10 weeks following delivery. There was no polyuria or polydipsia. On examination she appeared unwell and distressed, but was afebrile. The blood pressure was 110/80 mmHg and pulse 80/min supine, and 100/70 mmHg and 110/min respectively when upright. The remainder of the physical examination was normal; in particular, visual fields and fundoscopy were both normal. Investigation showed normal haemoglobin, white cell count and platelets. A biochemical profile revealed plasma total calcium of 3.12 mmol/l (2.00–2.50), albumin 39 g/l (37–52), phosphate 0.73 mmol/l (0.75–1.35) and alkaline phosphatase 90 U/l (30–100). Other biochemistry included plasma sodium 141 mmol/l (137–143), potassium 3.4 mmol/l (3.2–4.3), chloride 105 mmol/l (102–111), bicarbonate 24 mmol/l (22–31) and creatinine 0.094 mmol/l (0.070–0.100).

She was judged clinically to be hypovolaemic. A provisional diagnosis of primary hyperparathyroidism was made with differential diagnosis of Addison's disease and panhypopituitarism. Following rehydration with 0.9% saline she improved subjectively and the plasma total calcium decreased to 2.61 mmol/l (albumin 31 g/l). Twenty-four hours after saline infusion was stopped she again became unwell and nauseated with a blood pressure of 80/60 mmHg in the supine position; the plasma total serum calcium remained at 2.67 mmol/l (albumin 35 g/l). She was started on dexamethasone and fludrocortisone; her nausea abated quickly, she felt well subjectively and the blood pressure stabilized at 115/70 mmHg.
Shortly after admission, prior to administration of dexamethasone, a Synacthen stimulation test was performed, with Synacthen 250 μg given by intramuscular injection. The baseline cortisol was 35 nmol/l with a one-hour post Synacthen level of 45 nmol/l. Other hormone measurements were as follows: free thyroxine (fT4) 30 pmol/l (10–20), thyroid stimulating hormone (TSH) 0.2 mIU/l (0.5–4.0), PTH 0.2 nmol/l (1–6–9–0), follicle stimulating hormone (FSH) 2.7 IU/l (1.1–9.0), luteinizing hormone (LH) 1.2 IU/l (1.6–9.0), and prolactin (PRL) 0.2 mIU/l (0–5–4.0). The prolactin level decreased to within the reference range. Other hormone levels included: free thyroxine (fT4) 10 pmol/l and free triiodothyronine (fT3) values of 19.8 IU/l, 67.5 IU/l and 70 mIU/l respectively between 60 and 120 minutes. The baseline serum cortisol (Cort) was 290 nmol/l; there was minimal response to corticotroph failure. There was no history of a hypotensive episode during the peri-partum period to suggest Sheehan's syndrome as a possible cause. Pituitary adenoma characteristically causes progressive loss of hormonal function beginning with GH and FSH/LH and followed by TSH and ACTH (Snyder et al., 1979). In contrast, lymphocytic hypophysitis often results in loss of ACTH secretion alone, or ACTH and TSH with preservation of gonadotroph function (Cosman et al., 1989). This pattern may reflect selective destruction of pituitary cells by an autoimmune process.

Thyroid function at the time of the triple function test showed a fT4 at the lower end of the reference range and a normal TSH, with normal TSH response to TRH. The previous mildly hyperthyroid results probably reflect mild transient thyroiditis either related to the post-partum period or associated with lymphocytic thyroiditis (Cosman et al., 1989). Confirmation with a radioisotope uptake scan was not performed in the acute stage of her illness. Thyroid antibodies were not measured.

The prolactin level decreased to within the reference range. Although menses have not returned by 18 months post partum, she remains well otherwise.

**Discussion**

Although histological confirmation was not available, lymphocytic hypophysitis seems the likely diagnosis in a patient presenting in the post-partum period with selective corticotroph failure. There was no history of a hypotensive episode during the peri-partum period to suggest Sheehan's syndrome as a possible cause. Pituitary adenoma characteristically causes progressive loss of hormonal function beginning with GH and FSH/LH and followed by TSH and ACTH (Snyder et al., 1979). In contrast, lymphocytic hypophysitis often results in loss of ACTH secretion alone, or ACTH and TSH with preservation of gonadotroph function (Cosman et al., 1989). This pattern may reflect selective destruction of pituitary cells by an autoimmune process.

The unusual feature of this case was the severe hypercalcaemia. Primary hyperparathyroidism was excluded by the suppressed serum PTH level. It is unlikely that the hypercalcaemia was secondary to the thyrotoxicosis, since the hyperthyroidism was both mild and transient. The normal serum electrolytes gave no clue as to the cause of the hypercalcaemia and it was the clinical evidence of hypotension that pointed to adrenal insufficiency, and the non-response of cortisol to Synacthen stimulation that confirmed it. The serum calcium normalized with rehydration and steroid replacement; this provides further confirmation that the hypercalcaemia was not a consequence of thyrotoxicosis. The aetiology of the hypercalcaemia in adrenal insufficiency has not been fully elucidated, but is likely to be multifactorial.

Firstly, the hypovolaemia and the consequent reduction in glomerular filtration rate (GFR) are thought to result in a reduction in the calcium filtered in the glomerulus as well as an increase in proximal tubular reabsorption of sodium and calcium (Walker & Davies, 1981; Muls et al., 1982). These mechanisms are thought not to be directly mediated by adrenal hormone deficiency but to be secondary to the

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**Table 1 Results of triple function test**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>Ref. intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>4.2</td>
<td>1.7</td>
<td>2.0</td>
<td>3.3</td>
<td>3–5.5 mmol/l</td>
</tr>
<tr>
<td>fT4</td>
<td>10</td>
<td>10–20 pmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>2.6</td>
<td>16</td>
<td>12</td>
<td>6.8</td>
<td>0.5–4.0 mIU/l</td>
</tr>
<tr>
<td>Cortisol</td>
<td>290</td>
<td>230</td>
<td>310</td>
<td>190</td>
<td>140–690 mIU/l</td>
</tr>
<tr>
<td>GH</td>
<td>12</td>
<td>11</td>
<td>63</td>
<td>70</td>
<td>&lt;13.5 mU/l</td>
</tr>
<tr>
<td>PRL</td>
<td>640</td>
<td>1317</td>
<td>1114</td>
<td>832</td>
<td>&lt;400 mU/l</td>
</tr>
<tr>
<td>LH</td>
<td>5</td>
<td>56.9</td>
<td>67.5</td>
<td>54.5</td>
<td>1.6–9.9 mU/l</td>
</tr>
<tr>
<td>FSH</td>
<td>5.9</td>
<td>15.2</td>
<td>19.5</td>
<td>19.8</td>
<td>1.1–9.0 mU/l</td>
</tr>
</tbody>
</table>
consequent volume depletion, and hence correctable by rehydration of the patient. Our patient was unusual in that she had secondary adrenal failure with presumably intact mineralocorticoid function. She was hypovolaemic on presentation and the hypercalcaemia responded partially to intravenous saline infusion. This supports the existing evidence which suggests that hypovolaemia and reduced GFR contribute to the aetiology of hypercalcaemia.

However, at least one report suggests that this may not be the entire explanation for the reduced calcium excretion (Muls et al., 1982). Although the reduction in calcium excretion attributed to reduced calcium delivery to the glomerulus is completely corrected by volume repletion, the increased proximal tubular calcium reabsorption is not fully reversed by volume repletion, and normalizes only after glucocorticoid replacement (Muls et al., 1982). The reversal of increased calcium reabsorption in the proximal tubules is probably secondary to the sodium retention produced by glucocorticoids, which results in suppression of sodium and calcium reabsorption in the proximal tubule.

The second mechanism in the aetiology of hypercalcaemia associated with adrenal insufficiency is an increase in calcium efflux from bone into the circulation (Jowsey & Simons, 1968; Montoli et al., 1992). This represents a significant component of the aetiology of the hypercalcaemia (Muls et al., 1982). Calcium excretion, although inappropriately low for the serum calcium concentration in these patients, is in fact increased in absolute terms indicating increased calcium input into the circulation (Montoli et al., 1992). The calcium release from bone in this condition is not osteoclast mediated; bone histology has shown no evidence of increased osteoclastic activity; remodelling activities were actually reduced (Montoli et al., 1992). The presence of glucocorticoid receptors on bone cells has prompted the suggestion that physiological amounts of glucocorticoid hormones are necessary for the acquisition and preservation of the differentiated state in osteoblasts (Raisz & Kream, 1983). However, it is not clear whether glucocorticoid deficiency is the sole factor responsible for the increased calcium efflux from bone.

It has been shown in dogs that increased calcium mobilization from bone in the hypoadrenal state is thyroxine dependent; that is, adrenalectomized dogs develop hypercalcaemia only in the presence of the thyroid gland (Jowsey & Simons, 1968). Thus it may be that thyroxine is the factor causing increased calcium mobilization, with glucocorticoids in physiological concentrations inhibiting this action. Conversely, it has been suggested that glucocorticoid deficiency leads to release of calcium from bone either by direct action on bone cells or mediated by a decrease in pH in the presence of thyroxine which is necessary for maintenance of normal bone cell activity (Jowsey & Simons, 1968).

Hypercalcaemia is not a recognized feature of hypoadrenalism secondary to pituitary failure; in these patients secondary hypothyroidism often accompanies hypoadrenalism. Lymphocytic hypophysitis is unusual in that selective corticotroph failure is not uncommon in the presence of normal thyrotroph function. In fact the autoimmune process may extend to the thyroid gland causing thyroiditis and hyperthyroidism in the presence of secondary hypoadrenalism, as was probably the case in our patient. There have been two patients previously described with lymphocytic hypophysitis who had isolated corticotroph failure and secondary hypoadrenalism together with hyperthyroidism due to thyroiditis, and who presented with hypercalcaemia (Richtsmeier et al., 1980; Jensen et al., 1986). These clinical observations support the theory that thyroid hormone action is important in the aetiology of the hypercalcaemia of hypoadrenalism.

Note added in press
A sample taken 10 months after presentation was negative for anti-pituitary antibody when measured by Dr Patricia Crock (Crock et al., 1993) using an immunoblotting assay.

References

**Commentary**

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Hypercalcaemia has been described in Addison’s disease (Leeksma et al., 1957) and following bilateral adrenalectomy for Cushing’s disease (Sprague et al., 1953) but it is not a well recognized feature of pituitary failure. The accompanying Case of the Month illustrates a third reported case of hypercalcaemia occurring with isolated corticotrophin failure due to lymphocytic hypophysitis. All three cases had an associated hyperthyroidism and Vasikaran et al. (1994) highlight the possible role of thyroid hormones in the development of hypercalcaemia in cortisol deficiency. One of the four hypercalcaemic patients with Addison’s disease described by Leeksma et al. (1957) was hyperthyroid and in the recent report by Miell et al. (1991) hypercalcaemia was precipitated by correction of hyperthyroidism with thyrroxine. These isolated observations that thyroid hormone may have a pivotal role in the hypercalcaemia of cortisol deficiency are supported by experimental evidence in dogs (Jowsey & Simons, 1968) showing that an intact thyroid but not parathyroid gland was necessary for the development of the hypercalcaemia of cortisol deficiency.

Although hypotension, hypovolaemia and a reduction in the glomerular filtration rate have been shown to be responsible in part for the hypercalcaemia, correction of hypovolaemia alone does not fully correct hypercalcaemia which remains between 2.6 and 2.9 mmol/l (Vasikaran et al., 1994; Muls et al., 1982; Walker & Davies, 1981).

The hypercalcaemia of cortisol deficiency is unstable and Parfitt (1979) uses the term disequilibrium hypercalcaemia to describe a progressive rise in serum calcium with time as a consequence of a disparity between bone resorption and formation leading to an increased influx of calcium into the extracellular fluid. Severe hypercalcaemia results if there is a limited capacity of the kidney to excrete calcium. Most commonly this arises because an ever increasing serum calcium impairs distal tubular function and the ability to conserve salt and water. The increase in sodium reabsorption which then occurs in the proximal renal tubule is linked to calcium and further exacerbates hypercalcaemia.

Addison’s disease provides all these renal conditions de novo and any factor which increases the influx of calcium into the extracellular fluid from bone or gut can produce a rapid and life threatening rise in serum calcium (see Miell et al., 1991). The hypothesis must be that cortisol deficiency renders the bone more sensitive to thyroid hormones which are known to stimulate bone resorption. Mundy et al. (1976) have shown that thyroid hormones stimulate bone resorption in tissue culture and indomethacin and cortisol inhibit this action. Since cortisol can inhibit prostaglandin production, and thyrloxine induced bone resorption in mouse calvaria is partially dependent upon endogenous prostaglandin production (Klaushofer et al., 1989), a mechanism could be postulated for the interaction of these two hormones on bone.

Studies in the mouse have shown that bone resorption induced by thyroid hormones occurs via a receptor mediated mechanism (Krieger et al., 1988). Whether cortisol deficiency produces an up regulation of thyroid hormone receptors in bone or modifies post receptor events deserves further study.

**References**


