of aldosterone to its usual trophins. The complete loss of aldosterone production seen in examples of gross 11β-hydroxylase deficiency is probably secondary to the marked over production of deoxycorticosterone that leads to independent mineralocorticoid action of this hormone with secondary suppression of the renin/angiotensin/aldosterone axis.

In conclusion, we describe a novel splice-site mutation in CYP11B1 that results in partial 11β-hydroxylase deficiency manifested as XX masculinization when combined with the Q56X mutation.

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References


Isolated ACTH deficiency presenting as severe hypercalcaemia

A 64-year-old Australian woman of Indian descent presented with altered conscious state and progressive weakness on the background of a 2-month history of nausea and vomiting, weight loss (9 kg), lethargy, and low grade fever. Significant history included premature menopause at age 38 after two uncomplicated deliveries. There was no history of tuberculosis. Physical examination revealed only a small nontender multinodular goitre. Her corrected serum calcium was 3.29 mmol/l (NR 2.1–2.6), phosphate, 1.78 mmol/l (0.8–1.5), PTH 0.9, pmol/l (1.1–7.7), and 25OH-vitamin D, 19 nmol/l (50–150), with normal alkaline phosphatase and renal function. Angiotensin-converting enzyme level was normal. Her TSH was 0.01 mIU/l (0.3–5.0), fT4, 20.1 pmol/l (9–19), and fT3, 6.2 pmol/l (1.1–5.2). Her TSH receptor antibodies were 1 U (% 15), antithyroid peroxidase antibodies, 10 U/l (% 35), and her antithyroglobulin antibodies, 446 U/l (% 40). Thyroid ultrasound confirmed a small multinodular goitre with several subcentimetre nodules. A thyroid uptake scan was not performed, as she had received intravenous iodine contrast during a computed tomography (CT) scan performed by her primary physician for investigation of her weight loss 10 days prior to admission; this scan was reported to be normal. Her serum calcium improved with hydration to 2.70 mmol/l, but she remained weak and confused. During the first week of her admission, she was reviewed by multiple specialties with multiple laboratory and imaging studies, but the aetiology of her hypercalcaemia remained elusive. Ultimately, her serum cortisol and ACTH were measured and found to be repeatedly undetectable. Cortisone replacement led to prompt resolution of her symptoms, and corrected serum calcium fell to 2.21 mmol/l with no other medical therapy. Her pituitary function was otherwise normal for a postmenopausal woman: GH, 2.7 mU/l (0–20); IGF-1, 27.7 nmol/l (14.3–37.2); FSH, 40.6 IU/l (16.8–114); LH, 15.8 IU/l (11.5–58); oestradiol < 20 pmol/l; and PRL, mIU/l 508 (60–420). When clinically euoalcaemic, her renin level was 9.1 mIU/l (7–76), consistent with preserved mineralocorticoid function. One week after admission, her thyroid hormones had spontaneously normalized: fT4 was 18 pmol/l and her fT3 was 4.2 pmol/l, while her TSH remained low at 0.03 mIU/l. Although the initial brain CT and magnetic resonance imaging (MRI) were reported to be normal, a dedicated pituitary MRI showed a partial empty sella with normal stalk. She was discharged 5 days after initiation of steroid replacement, which was rapidly weaned to oral cortisone acetate maintenance. Corrected serum calcium was 2.30 mmol/l at discharge, and she was commenced on oral ergocalciferol. When she was reviewed 2 months after initiation of her steroid replacement, thyroid function tests and serum calcium were normal: TSH, 3.2 mIU/l; fT4, 9.8 pmol/l; fT3, 3.9 pmol/l; and corrected serum calcium, 2.35 mmol/l. Serum cortisol and ACTH levels determined 24 h after her last cortisone acetate dose remained undetectable.

While hypercalcaemia is well described in Addison’s disease, it is not a recognized feature of hypoadrenalism due to pituitary failure. Cortisol deficiency causes hypercalcaemia by two mechanisms: increased renal tubular calcium absorption and increased calcium release from bone.1 Hypovolaemia augments renal calcium retention and is more prominent in primary adrenal failure because of coexisting mineralocorticoid deficiency. Furthermore, coexistence of secondary hypothyroidism in secondary adrenal failure may prevent hypercalcaemia, as thyroid hormone appears necessary for the development of hypercalcaemia in the setting of cortisol deficiency. Cortisol inhibits thyroid hormone-mediated bone turnover in vitro.2 Adrenalectomized dogs develop severe hypercalcaemia, which is

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Fig. 1 Precipitation of hypercalcaemia and acute illness by thyrotoxicosis.

prevented by concomitant thyroideotomy. Furthermore, commencement of thyroxine for primary hypothyroidism can cause life-threatening hypercalcaemia in patients with untreated Addison’s disease. Our patient’s mild thyrotoxicosis per se is unlikely to explain the severity of hypercalcaemia. In a report of 437 patients with thyrotoxicosis, 8-5% had serum calcium levels above 2·65 mmol/l and the highest calcium of 2·8 mmol/l was found in a patient with co-existing primary hyperparathyroidism.

While the precise aetiology of the thyrotoxicosis in our patient remains uncertain, we suspect iodine contrast-induced thyrotoxicosis in a pre-existing multinodular goitre. This is supported by the self-limiting, transient nature of the thyrotoxicosis, as well as by the absence of clinical or laboratory features of Graves’ disease, subacute thyroiditis or Hashimoto’s thyroiditis.

Her hypovitaminosis D is likely to reflect the combination of diet, ethnicity, illness and latitude; a not uncommon finding in this context in Melbourne. The low 25OH-vitamin D level is therefore probably an incidental finding, largely independent of the presenting problems: a not uncommon finding in this context.

We found only five case reports of secondary hypoadrenalism presenting with hypercalcaemia. All cases, as with our patient, had isolated ACTH deficiency with concomitant transient thyrotoxicosis and low/ suppressed PTH levels, with serum calcium levels ranging from 3·1 to 3·7 mmol/l.

Similar to our experience, hydration improved calcium levels, but normocalcaemia was achieved only with cortisone replacement. Four of these published cases occurred in women in the peripartum period. The underlying diagnosis was lymphocytic hypophysitis, which was proven by biopsy in two cases. We speculate that transient thyrotoxicosis may have precipitated our patient’s acute presentation by two mechanisms, first, by accelerated cortisol clearance, and second, by the development of severe hypercalcaemia (Figure 1). Thus, cortisol and thyroid function should be measured in unexplained PTH-independent hypercalcaemia.

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Secondary adrenal failure and secondary amenorrhoea following hydromorphone treatment

A 32-year-old female patient presented with fatigue, weakness, postural hypotension, dizziness and secondary amenorrhoea for 3 months. The patient’s medical history revealed chronic pain syndrome (DSM-III-R) lasting 2 years. Four months before presentation, a pain clinic changed the analgesic treatment to hydromorphone 32 mg b.i.d. and up to 2·6 mg q.i.d. as single doses. Upon physical examination the patient (176 cm, 60 kg; body mass index, 19·4 kg/m²) was thin and looked unwell. Routine haematological and biochemical findings were normal. However, basal concentrations of plasma ACTH (1·8 pmol/l, normal range 2·0–11·0) and serum cortisol (18 nmol/l, normal range 130–630) as well as mean 24-h urinary free cortisol excretion (18 nmol/l, normal range 33·6–252) were decreased. Peak responses of serum cortisol to ACTH 250 µg (316 nmol/l, normal > 550 nmol/l) and during an insulin tolerance test (ITT) with 0·5 IU insulin per kg body weight (334 nmol/l, normal > 550 nmol/l) were reduced. During the ITT, adequate hypoglycaemia was achieved, with a plasma glucose level of 32 mg/dl and hypoglycaemic symptoms (trembling, sweating and pounding heart). Peak growth hormone response was within the low normal range (5·4 µg/l, normal 5·3–42·5). Furthermore, oestradiol levels were diminished (58 pmol/l, normal range 110–370) with LH (2·7 IU/l, normal range 2–10) and FSH (6·0 IU/l, normal range 2–12) concentrations within the normal range. The basal concentrations of the other anterior pituitary hormones were within the normal range. These findings were consistent with secondary adrenocortical insufficiency and secondary amenorrhoea due to hypogonadotrophic hypogonadism. Magnetic resonance imaging of the pituitary gland revealed no abnormal findings. The patient did not report traumatic brain injury, had not received cranial irradiation, nor did she take any glucocorticoid replacement.

During and after reduction of the hydromorphone treatment, we observed a marked and stable increase of the serum and urinary concentrations of cortisol and plasma levels of ACTH (Fig. 1a) as well as of LH, FSH, and oestradiol levels (Fig. 1b). Plasma levels of hydromorphone and morphine were measured during the opioid reduction. Morphine equivalent plasma levels [sum of morphine and (hydromorphone*7,5)] were significantly negatively correlated with

References