

Case Report

Does critical illness cause reversible Cushing's like syndrome? A case study of two case reports and review of the literature

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An activation of the hypothalamic-pituitary-adrenal axis (HPA) and elevated cortisol levels are common during critical illness. Clinically evident Cushing's syndrome, triggered by life threatening illness, has not been previously reported. We describe two patients with adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome, which developed during the life threatening illness and later spontaneously remitted. The impact of the acute and prolonged phase of critical-illness on the function of HPA axis with its complex neuroimmunoendocrine dynamics has been reviewed.

Key words: Adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome, hypothalamic-pituitary-adrenal axis, critical illness.

INTRODUCTION

The release of cortisol in both acute and chronic phases of critical illness is essential for cardiovascular, metabolic and immunologic homeostasis. In addition, cortisol suppresses the endogenous inflammatory response, protecting the acutely ill patient against the overresponse of this system. Cortisol also improves the haemodynamic status of the stressed individual by inducing fluid retention and by its enhanced inotropic and vasopressor response to catecholamines (Frank and Van den Berghe, 2004). The activated stress response system results in alteration in cardiovascular function, intermediary metabolism and immune mediated inflammation (Van den Berghe et al., 1998). In general, the degree of activation of hypothalamic-pituitary-adrenal (HPA) axis is proportional to the stress (Annane et al., 2000). The increased cortisol response to critical illness however does not usually result in clinical evidence of Cushing's syndrome. We report two patients who manifested evidence of glucocorticoid excess in response to the prolonged critical illness.

CASE REPORT

Case 1

A 56-year-old woman previously unknown to have diabetes was brought to the hospital severely ill. She had been unwell for one year prior to the presentation with polyuria, polydipsia and weight loss. Her weight was 38.0 kg at presentation. She had diabetic ketoacidosis (pH 6.91). Two weeks later, she presented with respiratory distress, and bilateral pulmonary emboli were demonstrated on computed tomography (CT) angiography. Her respiratory function improved within a week of commencement of anticoagulation therapy. Two months after the initial presentation, the patient was hospitalised because of continuing weight loss reaching a nadir of 27.5 kg and vomiting, despite insulin therapy. Before any treatment, the serum sodium was 120 mmol/l (reference range, 135 to 145), potassium 1.9 mmol/l (reference range, 3.2 to 4.5), chloride 75 mmol/l (reference range, 100 to 110), creatinine of 0.04 mmol/l (reference range, 0.05 to 0.1) and low blood glucose of 2.5 mmol/l (reference range, 3.0 to 7.8) and she had normal liver tests. A morning serum cortisol level was 915 nmol/l. A 5.2 × 3.6 × 5 cm cystic right ovarian mass was detected.

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The patient developed persistent hypokalemia (as low as 1.8 mmol/l) despite regular potassium replacement. A 24-h urinary free cortisol was elevated at 649 nmol/24 h (reference range < 150).

A total abdominal hysterectomy with the bilateral oophorectomy was performed and a benign serous cystic tumour was removed. The specimen was not stained for adrenocorticotrophic hormone (ACTH). The patient required regular potassium replacement with eight tablets of potassium chloride (8 mEq)/day. She did not appear cushingoid. A repeat 24 h urinary free cortisol (UFC) was 1757 nmol/24 h (reference range < 150). The 1 mg overnight dexamethasone test (DST) showed non suppression of the morning serum cortisol at 945 nmol/l; confirmed on the 48 h low dose dexamethasone suppression test (0.5 mg qid) with the morning serum cortisol of 417 nmol/l at 1600 h on day 2. The ACTH level was measurable at 44 ng/L (reference range, 10 to 50). The 48 h high dose dexamethasone suppression test (2 mg qid) showed non suppression of the serum cortisol at 477 nmol/l (1600 h, day 2) and 24 h UFC of 286 nmol/day suggesting the diagnosis of the ectopic ACTH secretion. The CT of the chest, abdomen and pelvis showed no tumor. Magnetic resonance imaging (MRI) of the pituitary was normal.

Four months after initial presentation, the patient had no cushingoid appearance but she developed a marked proximal myopathy. Blood pressure was 140/80. The biochemistry showed persistent hypokalemia with serum potassium in the range of 2.8 to 3.2 mmol/l despite regular potassium replacement. Her urinary cortisol/creatinine ratios were persistently elevated on consecutive early morning samples (median 205 $\mu\text{mol/mol}$ creatinine, range 47 to 303, $n = 16$ ref. range < 20).

Six months after initial presentation, the patient's clinical condition started to improve. Weight gradually increased to 49.5 kg, the proximal myopathy resolved and her need for potassium supplements disappeared. The overnight DST showed appropriate serum cortisol suppression from 222 to 47 nmol/l (0800 h); the 24 h UFC was within the normal range at 130 nmol/24 h. A series of subsequent urinary cortisol/creatinine ratios were predominantly normal (median 19 $\mu\text{mol/mol}$ creatinine, range 14 to 40, $n = 14$; reference range < 20). She remains well with insulin treated diabetes ten years after initial presentation with a weight of 50 kg.

Case 2

Three weeks after presenting obtunded with *Staphylococcus aureus* septicaemia and an extensive subdural empyema, a 74 years female, developed severe (190/90-205/105) hypertension despite treatment with maximal doses of four antihypertensive agents and new hypokalemia [2.2 to 3.1 mmol/l (reference range, 3.2 to 4.5)] simultaneously. Her hypertension was previously

well controlled with amlodipine 5 mg a day and quinapril 20 mg a day. The renal function was normal, serum albumin was 21 g/L 6 (reference range, 33 to 47). She did not have cushingoid appearance. Her postoperative period was complicated by multiple pulmonary emboli and a prolonged pneumonia, which required intubation and mechanical ventilation for a one week period.

Her midnight serum cortisol was 381 nmol/l. The 1 mg overnight dexamethasone test showed non suppression of the morning (0800 h) serum cortisol of 798 nmol/l, confirmed by 48 h dexamethasone at 0.5 mg 6 h with raised serum cortisol of 427 nmol (0800 h). An overnight high dose 8 mg dexamethasone test showed suppression of serum cortisol to 81 nmol/l. The ACTH level was measurable at 14 to 34 ng/L (reference range, 10 to 50). The CT pulmonary angiogram also demonstrated a 2.5 cm left adrenal mass. Pheochromocytoma and aldosterone secreting tumour were excluded.

An expectant course was followed. Four months after initial presentation, her BP settled to pre-morbid levels and need for potassium supplements disappeared. Twelve months later her 24 h urinary free cortisol was normal at 87 nmol/24 h (reference range <150). The overnight 1 mg dexamethasone suppression test showed suppression of the morning cortisol to 35 nmol/l, confirming the resolution of Cushing's syndrome. The CT adrenal showed no change in the size of the adrenal mass. The patient remains well four years after the episode.

DISCUSSION

The appearance of clinically evident Cushing's syndrome in response to acute illness is not a recognized phenomenon. Excess cortisol secretion was sought in both patients because of the appearance of marked hypokalemia in association with hypertension and/or proximal myopathy. The ACTH was measurable in both patients indicating an ACTH-dependent form of Cushing's syndrome.

The absence of obvious cushingoid phenotype in combination with prominent hypercortisolemia was consistent with a sudden development of the syndrome, suggestive of ectopic ACTH secretion. Both patients had otherwise unexplained severe hypokalemia (in one case associated with hypertension) suggesting saturation of the intracellular enzyme 11 beta hydroxysteroid dehydrogenase type 2 (11beta-HSD2), which inactivates cortisol to cortisone and activation of the mineralocorticoid receptor (Stewart and Krozowski, 1994). The development and persistence of the syndrome with demonstrable excess cortisol production weeks and months after the acute illness had settled and its spontaneous resolution is noteworthy.

An appropriate activation of the hypothalamic-pituitary-adrenal axis is seen in critical illness, and both high and low cortisol levels have been associated with increased

mortality (Schuetz and Mueller, 2006; Hamrahian et al., 2004). The increases in cortisol are not usually associated with the clinically evident syndrome. The secretory activity of the hypothalamic-pituitary-adrenal (HPA) axis is maintained in the acute (hours to a few days) phase of critical illness. The hypercortisolism in this setting provides energy, protects the body and is reflected by increased gluconeogenesis, maintenance of intravascular volume and inhibition of the acute inflammatory reactions. However, when the disease becomes prolonged (lasting many days or weeks), there is a uniformly reduced pulsatile secretion of anterior pituitary hormones with active involvement of non-ACTH mediated pathways. In line with loss of hypothalamic ACTH control and decrease in plasma ACTH concentration, the diurnal variation in cortisol secretion disappears.

Both described subjects developed pulmonary emboli within two weeks of their initial presentation. Ectopic ACTH syndrome in majority of cases is caused by an intrathoracic neoplasm which secretes ACTH precursors (Stewart et al., 1989). Normal human lung produces small amount of the parent compound proopiomelanocortin (POMC) (White et al., 1990). It is believed that overexpression of gene responsible for POMC production in the setting of malignancy causes increase in POMC levels which is cleaved to ACTH and pro ACTH (Stewart et al., 1994), but the posttranslational processing of the peptides is unclear. Hypothetically pulmonary emboli might have incited a similar reaction which resulted in production of ACTH precursors by the lungs and has subsequently resolved as the process healed. Alternatively, an inflammatory reaction in the lungs due to pulmonary emboli could have caused secretion of inflammatory cytokines which can also stimulate the HPA axis (Chrousos, 1995). Alternately, transient Cushing's syndrome might have been related to suprapituitary stimulation of corticotrophs by corticotroph releasing hormone (CRH) and vasopressin that was induced by illness through autonomic nervous system which modulates CRH secretion and represents the origin of a final common pathway for neurohormonal regulation of ACTH-corticosterone release (Van Loon et al., 1989).

Most critically ill patients will usually have many reasons to explain potassium deficits, myopathy and even hypertension. The possibility that excess cortisol levels may be a contributory factor should be remembered in such patients. Interpreting cortisol levels in critically ill patients can be difficult and even substantial and non-suppressible elevations in cortisol may persist many weeks and possibly months after the acute illness has subsided. Clinicians should develop an awareness of this phenomenon, which may help them with the management of often very complex clinical presentations.

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