J Anesth (2011) 25:431–434
DOI 10.1007/s00540-011-1118-3

CLINICAL REPORT

Catecholamine-resistant shock and hypoglycemic coma after cardiotomy in a patient with unexpected isolated ACTH deficiency

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Received: 13 August 2010 / Accepted: 17 February 2011 / Published online: 13 March 2011

Abstract Isolated adrenocorticotropic hormone (ACTH) deficiency is an extremely rare disease in which ACTH-producing cells of the pituitary gland are selectively damaged. The resulting decline in ACTH production and secretion results in chronic secondary adrenocortical insufficiency. The patient in this case did not present with adrenal insufficiency symptoms prior to surgery. However, after cardiotomy under extracorporeal circulation, the patient lapsed into a catecholamine-resistant shock and hypoglycemic coma. Acute adrenal insufficiency was strongly suspected, and the patient was diagnosed with isolated ACTH deficiency after careful examination. Because the demand for cortisol increases after highly invasive surgeries, cortisol supplementation therapy is essential for patients with complications from isolated ACTH deficiency. There is a high risk of a lethal outcome when surgery is carried out without a diagnosis, as in this case. Therefore, cortisol must be supplemented without delay when acute adrenal insufficiency is suspected during the perioperative period.

Keywords ACTH · Cortisol · Adrenal insufficiency · Hypoglycemia · Hypotension

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Introduction

Adrenocorticotropic hormone (ACTH) is released from the anterior pituitary gland and is an important hormone of the hypothalamic–pituitary–adrenocortical axis. Isolated ACTH deficiency is a condition characterized by a decline in ACTH secretion. Under normal conditions, this disease shows nonspecific symptoms, including general malaise, decreased mental function, gastrointestinal symptoms, hypotension, and hypoglycemia; therefore, cases commonly go undiagnosed. However, under stressful conditions, a patient's life may suddenly be at risk because of the inability to secrete ACTH in response to the stressor [1]. Here we report a cardiotomy under extracorporeal circulation in a patient who suffered complications from isolated ACTH deficiency.

Case report

The patient was a 59-year-old man (height 173 cm, weight 70 kg) with chronic heart failure due to mitral insufficiency, which had been treated with pharmacotherapy (enalapril maleate, isosorbide mononitrate, carvedilol, lafutidine, trimebutine maleate, digoxin, furosemide, and spironolactone). Due to repeated and frequent heart failures, the patient was transferred to this hospital for surgery. Apart from chronic heart failure, the patient's past medical history and family history were unremarkable. Symptoms upon admission included a systolic blood pressure of 80–100 mmHg, atrial fibrillation, and a slight yellowing of the skin and bulbar conjunctiva. During the preoperative examination, findings were within normal ranges other than slightly impaired hepatorenal function associated with chronic heart failure and reduced fasting glucose levels

(74 mg/dl). Chest X-rays revealed a pulmonary artery shadow and a higher cardiothoracic ratio (57%), and an electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. No abnormality in wall motion was detected (left ventricular ejection fraction 85%) by transthoracic echocardiography. Mitral insufficiency and a slight tricuspid insufficiency, which accompanied posterior leaflet prolapse due to left atrial enlargement and ruptured chordae tendineae of the mitral valve, were observed. Ultimately, we decided to treat the patient with mitral and tricuspid valvuloplasty and Maze surgery.

Intramuscular injections of morphine hydrochloride (5 mg) and hydroxyzine (25 mg) as preanesthetic medication were given 30 min prior to surgery. At initiation of surgery, blood pressure was 100/50 mmHg, heart rate 80–90/min with atrial fibrillation, and the patient was lucid. Anesthesia was induced by target-controlled infusion (TCI) of propofol (2 μg/ml) and intravenous (IV) injection of fentanyl (100 μg). The trachea was intubated after IV injection of vecuronium (0.1 μg/kg). Propofol (1–2 μg/ml, TCI) and fentanyl (100 μg, IV injection) were administered as needed to maintain the bispectral index (BIS) between 40 and 60; IV injections of vecuronium were administered intermittently. Hemodynamics were stable, and mitral and tricuspid valvuloplasty and Maze surgery were carried out as scheduled under cardiopulmonary bypass. Immediately after detachment from the heart–lung apparatus, the temporary dual chamber (DDD) pacing indicated a heart rate of 90/min and cardiac index of 2.3 L/min/m^2, regurgitation in mitral and tricuspid valves was eliminated as assessed by transesophageal echocardiography, and wall motion was normal. Thirty minutes after detachment, systolic blood pressure remained in the 40–50 mmHg range. Dopamine was increased to a maximum of 5 μg/kg/min. Systolic blood pressure increased and stabilized at 90–100 mmHg by the time the surgery was complete. Duration of surgery, cardiopulmonary bypass, and anesthesia was 330, 205, and 425 min, respectively. Plasma electrolyte data are shown in Table 1. No hyponatremia or hyperkalemia was observed during the perioperative period, and cortisol and ACTH levels were below the normal range. After surgery, the patient was taken to the ICU.

Three hours after entry into the ICU, systolic blood pressure decreased to the 70–80 mmHg range, and the cardiac index also declined. At this time, central venous pressure (CVP) was 4 mmHg and mean pulmonary artery pressure (MPAP) 14 mmHg. Preload was inadequate; infusions of plasma substitute and dopamine (5 μg/kg/min) were continued. Subsequently, arterial pressure increased and cardiac index was maintained at 2.4–2.6 L/min/m^2; however, systolic blood pressure gradually declined to 40–50 mmHg 6 h after entry. Given the possibility of anaphylactic shock due to pharmacological agents, all pharmacological agents were discontinued except catecholamines and vasoactive agonists. Dopamine was increased to 8 μg/kg/min, but blood pressure remained low and urine output also gradually declined. Twelve hours later, we confirmed acute renal failure [blood urea nitrogen (BUN) 31.9 mg/dl, serum creatinine (Cr) 2.42 mg/dl]. Vasodilatory shock was suspected based on these findings. Noradrenaline (0.1 μg/kg/min) was added to increase vascular resistance, but no pressor response was detected. No change was observed with coadministered vasopressin (2 U/h). At this point, we considered the possibility of relative adrenal insufficiency in response to invasive surgery and administered hydrocortisone 100 mg IV every 8 h. Systolic blood pressure returned to the preoperative value of approximately 100 mmHg with dopamine alone (4 μg/kg/min). Dopamine was terminated and urine output increased by postoperative day 3. The patient left the ICU on postoperative day 5.

Renal failure rapidly improved after a peak BUN of 75.64 mg/dl and Cr of 4.8 mg/dl on postoperative day 8. Other abnormal physical findings and test results steadily improved. However, the patient experienced impaired consciousness on postoperative day 12, and marked hypoglycemia (blood glucose 44 mg/dl) was detected. Hypoglycemic coma was suspected, and glucose was administered IV; consciousness was quickly restored. Thereafter, hypoglycemia occurred repeatedly, but the pattern of insulin secretion was normal. From these processes, we strongly suspected adrenal insufficiency and performed endocrinology tests. Table 1 shows serum ACTH and cortisol levels from samples obtained and frozen during the perioperative period. ACTH and cortisol levels did not increase during the peri- and postoperative periods. Data from the endocrine challenge test are shown in Table 2. Blood levels of ACTH and cortisol were both low; responses to the ACTH

Table 1 Perioperative serum cortisol, adrenocorticotropic hormone (ACTH), and electrolyte levels

Hormone	Normal range	Just after induction	At the end of CPB	2 h after surgery	12 h after surgery
Cortisol (μg/dl)	4–18	1.6	2.4	4.6	5.2
ACTH (pg/dl)	10–50	6.9	2.0	2.0	5.6
Sodium (mEq/L)	136–152	138	138	140	138
Potassium (mEq/L)	3.5–5.0	3.8	4.5	4.1	4.0

CPB cardiopulmonary bypass

Table 2 Endocrine challenge test

Hormone	Before endocrine challenge test	15 min	30 min	60 min	90 min
GH (ng/ml)	2.37	16.4	17.7	14.7	10.6
ACTH (pg/ml)	6.5	9.0	8.3	10.1	7.3
Cortisol (μg/dl)	0.7	0.7	0.8	1.0	1.0
LH (ml U/ml)	3.2	5.6	6.4	7.4	8.1
FSH (ml U/ml)	4.6	4.9	4.8	5.8	6.2
PRL (ng/ml)	36.5	74.5	84.8	79.8	75.9

GH growth hormone, *ACTH* adrenocorticotropic hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *PRL* prolactin

stimulation test [corticotropin-releasing hormone (CRH) load] and rapid ACTH test were low. Secretion of anterior pituitary hormones other than ACTH [growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL)] was normal. Based on these findings, the patient was diagnosed with isolated ACTH deficiency. Oral hydrocortisone (20 mg daily) was initiated on postoperative day 18. Adrenal insufficiency symptoms quickly improved, and renal function was nearly normal on postoperative day 21. The C-reactive protein (CRP) test was negative on postoperative day 31, and the patient was released on postoperative day 35.

Discussion

Isolated ACTH deficiency was first reported by Steinberg et al. [2] in 1954. The resulting decline in production and secretion of ACTH causes chronic secondary adrenocortical insufficiency. Although considered an extremely rare disease, the number of diagnosed cases is increasing because knowledge of the disease and detailed endocrinology testing have become more widespread [3]. In particular, incidence is relatively high among men at 40–60 years of age. Symptoms and signs of adrenal insufficiency are nonspecific, such as general malaise, decreased mental function, gastrointestinal symptoms, hypotension, and hypoglycemia; therefore, isolated ACTH deficiency often goes undiagnosed. In the absence of a correct diagnosis and supplementation therapy, powerful stressors such as external wounds, infections, surgery, or bleeding can trigger acute adrenal insufficiency, and the disease may become lethal [1]. In our case, we observed no preoperative symptoms or signs of adrenal insufficiency; however, early symptoms of general malaise and easy fatigability may have been masked by cardiac failure symptoms associated with mitral insufficiency. In addition, adrenal insufficiency symptoms and abnormal test results may have been mild in the absence of a stressor because of residual cortisol secretion. Therefore, the diagnosis of isolated ACTH deficiency was likely to be difficult.

In heart surgery carried out under cardiopulmonary bypass, cortisol has been reported to increase after detachment from the heart–lung apparatus and remain high until postoperative day 2, whereas ACTH peaks at 6 h after detachment and returns to normal within a day after surgery [4]. However, in our case, both cortisol and ACTH levels were below normal prior to anesthesia induction and remained low until 12 h after surgery, showing no increase after surgical invasion. Indeed, cortisol and aldosterone deficiencies are commonly observed in isolated ACTH deficiency [5, 6]. Furthermore, cortisol increases vascular reactivity to catecholamines and increases peripheral vascular resistance to raise blood pressure [7]. In our patient, cardiac function improved after cortisol supplementation therapy. Low cortisol levels may have caused the severe catecholamine-resistant hypotension despite adequate cardiac function.

Catabolic stress hormones (catecholamines and glucagon) are secreted in large amounts during the perioperative period and are likely to cause hyperglycemia via increased glycogen decomposition and gluconeogenesis [8]. In particular, marked hyperglycemia is observed after cardiotomy during cardiopulmonary bypass [9]. Inflammatory cytokines activate suppressors of cytokine signaling, which inhibits insulin signaling, further reducing the uptake of sugars into cells and promoting hyperglycemia [10]. These factors may have masked the hypoglycemia of isolated ACTH deficiency during the acute phase following surgery, delaying the detection of hypoglycemia until postoperative day 12, when the inflammatory response was declining.

We conclude that in rare cases of catecholamine-resistant shock or a hypoglycemic episode during the perioperative period of a cardiotomy under cardiopulmonary bypass, it is necessary to consider the possibility of isolated ACTH deficiency and immediately initiate cortisol replacement therapy.

References

1. de Luis DA, Aller R, Romero E. Isolated ACTH deficiency. Horm Res. 2008;49:247–9.
2. Steinberg A, Shechter FR, Segal HI. True pituitary Addison's disease, a pituitary unitropic deficiency; fifteen-year follow-up. J Clin Endocrinol Metab. 1954;14:1519–29.

3. Yamamoto T, Kamoi K. Prevalence of maturity-onset isolated ACTH deficiency (IAD) in 2005: Japanese cohort studies. Endocr J. 2008;55:939–41.
4. van Wezel HB, Zuurbier CJ, de Jonge E, van Dam EW, van Dijk J, Endert E, de Mol BA, Fliers E. Differential effects of a perioperative hyperinsulinemic normoglycemic clamp on the neurohumoral stress response during coronary artery surgery. J Clin Endocrinol Metab. 2006;91:4144–53.
5. Burke CW. Adrenocortical insufficiency. Clin Endocrinol Metab. 1985;14:947–76.
6. Shibutani Y, Ueo T, Takahashi S, Moriwaki Y, Yamamoto T. Effect of ACTH on renal excretion of purine bases in a patient with isolated ACTH deficiency. Clin Chim Acta. 2000; 294:185–92.
7. Ullian ME. The role of corticosteriods in the regulation of vascular tone. Cardiovasc Res. 1999;41:55–64.
8. Chernow B, Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, Fink MP, Lake CR, Fletcher JR. Hormonal responses to graded surgical stress. Arch Intern Med. 1987; 147:1273–8.
9. Carvalho G, Moore A, Qizilbash B, Lachapelle K, Schricker T. Maintenance of normoglycemia during cardiac surgery. Anesth Analg. 2004;99:319–24.
10. Ueki K, Kondo T, Kahn CR. Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. Mol Cell Biol. 2004;24:5434–46.