Case Report

Is this Acute Manifestation of Adrenal Crisis?

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Abstract

Adrenal crisis is a life threatening complication of both primary and secondary adrenocortical insufficiency. The diagnosis of adrenal crisis requires a high index of suspicion, such as circulatory collapse, refractory hypotension, and metabolic acidosis. The clinical features are because of both mineralocorticoid and glucocorticoid deficiencies. The primary and initial treatment is intravenous cortisol therapy, and saline (sometimes glucose). Case presentation was used in this 43 year old woman who presented with dizziness, anorexia, vomiting, generalized weakness, and lethargy. She had a history of recent tuberculosis infection and was commenced on antituberculosis therapy, rifampicin. Her biochemical profile was suggestive of impending adrenal crisis. Her chest X ray and computed tomography were grossly normal. The patient recovered completely and was discharged home with the resolution of her deranged metabolic and electrolyte derangements. Appropriate specialist care is vital in patients with adrenal crisis, coupled with initial aggressive fluid resuscitation and acid base balance and good intensive care.

Keywords: Addison's disease, adrenal crisis, adrenal insufficiency, adrenocortical crisis, primary adrenal insufficiency, primary adrenocortical insufficiency

Introduction

Adrenal crisis is an uncommon but acute life-threatening medical emergency that can occur in patients with secondary adrenal insufficiency, although less commonly than in patients with Addison's disease (primary adrenal insufficiency).[1-5] In all acutely unwell patients with circulatory collapse, hypernatremia, hyperkalemia, and metabolic acidosis, adrenal crisis must be suspected and treated based on clinical suspicion. The annual incidence rate in the UK is 8–14 crisis per 100 patient-years.[1,6] In Australia, it is 7.5 crisis per 100 patient years.[7] In two German studies incidence rate of 6.3–14 crisis per 100 patient years have been documented.[8,9] Mortality data from Addison's disease Swedish study showed increased all-cause mortality, at a relative risk of 2.19 and 2.86 for men and women, respectively.[4] However, the increased mortality seen in patients with adrenal insufficiency is partly due to adrenal crisis.[10] Adrenal crisis occurs in >50% of patients before the formal diagnosis of Addison's disease.[11] Early recognition and diagnosis of adrenal insufficiency are important in the prevention of premature mortality associated with adrenal crisis.[11] However, the symptoms of adrenal crisis are life-threatening and so delay or incorrect diagnosis is a frequent cause of preventable deaths.[12]

This review aims to emphasize the importance of early diagnosis and management of Addison's disease to avert adrenal crisis in the context of current evidence.

Case Presentation

The case report is aimed to discuss in detail the case of impending adrenal crisis and goal-directed management protocols in a patient who presented at a secondary care in the UK.

A 43-year-old woman was brought in by an ambulance to the emergency department with a history of dizziness, anorexia, vomiting, general weakness, and lethargy. There was no history of recent surgery or sepsis; however, she had a history of current infection with tuberculosis, of which she was commenced on antituberculous therapy, Rifampicin. There was no history of abdominal or back pain, and no

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unintentional weight loss. She had a background history of adrenal insufficiency of which she was placed on steroids. On examination, she was conscious, drowsy, and very lethargic with a Glasgow Coma scale of 14. She appeared mildly dehydrated but was not pale, not cyanosed, afebrile, and anicteric. Her pulse rate was 112 beat/min and blood pressure of 90/60 mmHg. There was no raised Jugular venous pressure. Heart sounds I and II were heard on auscultations. There was no pitting pedal edema. Her chest examination was unremarkable. Her oxygen saturation was 98% on room air, and breath sounds were normal. Abdominal examination was soft and nontender areas. The liver and spleen were normal and nonpalpable. The kidneys were not ballotable. Her blood biochemistry results were sodium 125 mmol/L, potassium 5.9 mmol/L, urea 13 mmol/L, bicarbonate 16 mmol/L, and glucose 3.9 mmol/L. A clinical diagnosis of adrenal crisis was made. Monitors and high flow oxygen through a rebreather mask was applied, and intravenous access gained. Her plasma ACTH was 25pmol/L (normal range 2.2-13.3pmol/L), serum cortisol was 130nmol/L (normal range 140-690nmol/L), serum aldosterone was 50pmol/L (normal range 100-450pmol/L) and plasma renin was 5.1mU/L (normal range 5.4-60mU/L). Septic screen blood was also taken, with inflammatory markers and blood cultures, midstream urine collection. The patient was started on intravenous fluids and steroids. A chest X-ray was unremarkable. Computerized tomography (CT) scan of the head was normal.

Discussion

Adrenal crisis is a symptomatic catecholamine-resistant state of shock in the presence of metabolic and electrolyte derangements. It can be insidious, gradual in onset, and is often not recognized in its early stages; however, can be life-threatening.[13] In healthy persons, endogenous cortisol secretion is usually elevated in response to stressful stimuli. However, in adrenal crisis, the physiological demand for these hormones exceeds the capacity of the adrenals to produce them in response to stressful events. It is particularly seen in patients with Addison's disease due to failure of the adrenocortical parenchymal tissue to produce glucocorticoid (cortisol) and mineralocorticoid (aldosterone) hormones.[14] Although glucocorticoid deficiency rather than mineralocorticoid is the predominant hormone deficiency in adrenal crisis,[15,16] either deficiency may herald the disease with failure of both hormones eventually. In addition, it can also occur in people who are undiagnosed with Addison's disease but have other endocrine disorders, such as hypothyroidism, hyperthyroidism, hypoparathyroidism, and type 1 diabetes mellitus (T1DM). An isolated increase in thyroid stimulating hormone on a background of normal triiodothyronine (T3) and/or thyroxine (T4) levels may be a feature of Addison's disease, and treatment with levothyroxine may precipitate adrenal crisis in this group of individuals.[17]

In patients with known Addison's disease, it is known that certain drugs or medications such as sedatives, narcotics, anesthetic agents, rifampicin, phenytoin, and phenobarbital increase the metabolism of cortisol and may precipitate Adrenal crisis. Other drugs-inducing adrenal crises include mitotane, etomidate, and ketoconazole, as a result of their adrenostatic properties.[13,18-20] In a shocked patient with hypernatremia, hyperkalemia, and hypoglycemia should raise a suspicion of acute adrenal crisis.

Adrenal crisis is a life-threatening illness, as the patient is acutely unwell and oftentimes in shock. Therefore, the patient should be transferred to the resuscitation room for appropriate management. Examination of the patient particularly over the exposed areas on mucous membranes and in skin creases (i.e., palmar creases), knuckles, and scars may reveal hyperpigmentation of the skin, as well as some areas of loss of pigmentation (i.e., vitiligo). Vitiligo may be suggestive of an ongoing autoimmune disorder. Usually, vitiligo is characterized by bilateral patchy and symmetrical areas of depigmentation of skin over the trunk or extremities, with surrounding skin being usually hyperpigmented. Skin hyperpigmentation caused by the stimulation of melanocyte-stimulating hormone by elevated high plasma adrenocorticotropic hormone (ACTH) levels may present in palmar and finger creases, knuckles, elbows and knee flexures, and areolar tissues. Buccal and nail bed pigmentations may occur.[13,21] Although in secondary adrenal insufficiency (which is caused by pituitary disease), ACTH levels are low rather than elevated, and hyperpigmentation is absent. However, adrenal crisis secondary to bleeding develop rapidly and does not normally display the classical hyperpigmentation.

Adrenal crisis can be difficult and challenging, particularly in patients without prior diagnosis of adrenal insufficiency. However, some distinctive but not pathognomonic symptoms of adrenal crisis [Table 1] are a consequence of the catecholamine-resistant shock.

Mental symptoms may include lethargy and confusion. Psychotic manifestations may occur on occasion.

Clinical diagnosis from presentations is very difficult, particularly with the absence of electrolyte and metabolic disturbances in addition to shock, which are nonspecific and are seen in other differential diagnoses.

Table 1: Common features seen in adrenal crisis

Gastrointestinal symptoms	Severe diarrhoea and vomiting
Metabolic symptoms	Hypoglycemia and neurocognitive unawareness
Electrolyte disturbances	Hyponatremia, hypochloremia, hyperkalemia, hypercalcemia and azotemia (abnormal renal function and elevated amounts of blood urea nitrogen)
Hemodynamic instability	Tachycardia or relative bradycardia, cardiac arrhythmias, refractory hypotension, orthostatic hypotension, circulatory shock and collapse
Acid-base disturbances	Metabolic acidosis

The pathophysiological causes are infection (in this case, tuberculosis) and medication with rifampicin. While tuberculosis can precipitate adrenal hemorrhages by the destruction of both cortices and medullae, rifampicin can precipitate Addisonian crisis by increasing the metabolism of cortisol. Precipitants of the adrenal crisis include intercurrent illnesses such as urinary tract infections (UTIs), flu-like illness, and septicemia, gastrointestinal infections such as *Escherichia coli* and herpes simplex, and dehydration. Fulminant sepsis with pseudomonas species and meningococcemia (Waterhouse–Friderichsen syndrome) also cause adrenal crisis. In these septicemic conditions, adrenal crisis is often sudden in onset, rapid progression and usually catastrophic. In one Swedish study, the relative risk of mortality in men and women from infectious disease was 6.6 (95% confidence interval [CI]: 2.6–15.2) and 5.6 (95% CI: 2.0–12.0), respectively.[4] In addition, the presence of diabetes, premature ovarian failure and/or asthma can precipitate adrenal crisis. Others include surgical removal of the adrenal glands, congenital adrenal hyperplasia, or adrenoleukodystrophy.[1,22,23] It is known that the early phase of thyroxine replacement in patients with adrenal insufficiency with concomitant hypothyroidism can precipitate adrenal crisis from its enhanced hepatic corticosteroid effects and increased cortisol demand.[17,24] In addition, patients whose corticosteroid therapies had been suddenly withdrawn after long-term administration can precipitate adrenal crisis. Similarly, patients who have not matched their therapy with the increase steroid demand of stressful situations such as trauma, surgery, and burns can manifest with adrenal crisis.

Hypotension, often orthostatic, is caused by the absence of the pressor effects of cortisol on vascular tone and by a decrease in cardiac output. As a result of aldosterone deficiency, sodium loss results from reduced aldosterone-mediated reabsorption of sodium in the distal renal tubules (loss of sodium in the urine) and increased intracellular shift of sodium, resulting in hypernatremia. Extracellular sodium loss depletes extracellular fluid volume and consequent decreased circulating blood volume, further worsening hypotension. Hypotension may trigger antidiuretic hormone (ADH) secretion with consequent water retention, resulting in a particularly significant life-threatening but transient pulmonary edema. This exacerbates the already existing hypernatremia. The hypernatremia may be exacerbated by hypotension-induced ADH secretion and water retention.

Hypovolemia, decreased cardiac output and decreased renal blood flow with azotemia as well as weakness, hypotension, and weight loss, may be related to sodium depletion. However, potassium retention caused by aldosterone deficiency and decreased renal potassium excretion may lead to hyperkalemia and cardiac arrhythmias.

However, loss of glucocorticoid hormones can accentuate hypotension, partly as a result of reduced sensitivity to angiotensin II and noradrenaline and perhaps reduced production of angiotensinogen. Intravenous fluid resuscitation and rehydration should also be instituted, but it is worthy to note that the hypotension will not respond to fluids until the glucocorticoid deficiency has been treated with intravenous steroids. Initial life-saving measures include the administration of hydrocortisone 100–200 mg intravenously as soon as the diagnosis is suspected. Monitor electrolytes and blood glucose closely.

Hypoglycemia is related to decreased cortisol-induced gluconeogenesis. Correct hypoglycemia and send blood for serum cortisol and ACTH levels in addition to thyroid function tests (TFTs). Electrocardiogram might show evidence of hyperkalemia. Do arterial blood gas analysis to assess the severity of the shock (metabolic acidosis). The loss of gluconeogenic effects of cortisol accounts for the early morning hypoglycemia usually seen after infections, fever, or alcohol ingestion. This is compounded following the loss of the counter-regulatory effect of cortisol after normal insulin secretion.

The diagnosis of adrenal crisis is based on a high index of suspicion, particularly in patients with refractory hypotension, on a background electrolyte, metabolic, and acid-base disturbances. Certain diseases are known to mimic adrenal crisis in the ED and general practitioner surgery. In the ED, radiological imaging, ultrasonography, and the degree of electrolyte derangements and circulatory shock can help identify the diagnosis. Gastroenteritis may initially present with similar features. However, a background history of adrenal insufficiency may help in differentiating viral or bacterial gastroenteritis. Azotemia can arise from acute renal failure secondary to hypovolemic shock and decreased renal blood flow. The past medical history may show prior history of adrenal insufficiency or adrenal failure and regular endocrinology clinic follow-ups. Patients with recurrent epigastric pain may have been incorrectly diagnosed with chronic gastric and duodenal ulcers and treated with proton pump inhibitors.[25] Endocrine disorders such as hypothyroidism and myxedema coma mimic adrenal crisis. Full blood count, TFTs, and gonadal function tests can be performed. Metabolic disturbances with acidosis from other causes, such as diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, and acute kidney injury, may have common features with adrenal crisis. Severe UTIs can cause nonspecific symptoms similar to adrenal crisis. However, a urinary dipstick will readily show the evidence of UTI. Others may have been misdiagnosed as having chronic fatigue syndrome or depression. However, in the presence of unexplained shock, it should be considered. Easy fatiguability can deepen into confusion and stupor. Therefore, these symptoms may suggest a high index of suspicion in the diagnosis of adrenal crisis. In addition, suspect bilateral adrenal hemorrhage in patients on anticoagulation agents with symptoms of adrenal crisis. Treat any underlying precipitants or infections, many advocate routinely giving broad-spectrum antibiotics such as intravenous cefuroxime 1.5 g immediately. However, arrange for an ultrasound of the adrenals when the patient is stabilized.

The management should be commenced in line with adult life support Guideline, as they present usually through the ED, with the stabilization of airway, breathing, and circulation, before commencement of definitive treatment. The treatment objectives include restoration of circulating blood volume, supplementing deficits in mineralocorticoids and glucocorticoids therapy, control of hyperkalemia, hypoglycemia and cardiac arrhythmias. Initially, hydrocortisone 100 mg should be administered intravenously. Repeat doses of hydrocortisone 100 mg every 6 h for first 24 h may needed. It is worthy to note that 400 mg of Solu-Cortef (hydrocortisone) is a high dose and should not be continued for >24 h, since the calculated need even in a severe crisis is closer to 200 mg. Too much hydrocortisone may lead to hypokalemia. Interestingly, such a high dose of hydrocortisone (i.e., 100 mg 6 hourly) has mineralocorticoid activity, and fludrocortisone is less important treatment at early management of acute adrenal crisis when patient is receiving high dose of hydrocortisone. When the gastric activity of the patient improves, oral fludrocortisone 100 mcg should be given. This has 400 times the mineralocorticoid effects of hydrocortisone to improve the hypovolemic shock, in addition to fluid infusion. However, fludrocortisone takes several days to attain the desired sodium-retaining ability. Therefore, continue to replace sodium with intravenous normal saline infusion, to restore circulating blood volume. Fluid restoration aids in controlling hyperkalemia by increased renal potassium excretion, otherwise hyperkalemia can be treated using calcium gluconate or chloride administration along with appropriate actrapid insulin doses. However, the clinician should be aware that patients with acute adrenal crisis are at an increased risk of severe hypoglycemia with this treatment regime and should be extremely cautious in giving insulin infusion to a patient with acute adrenal crisis. Therefore, the management should focus on intravenous fluids and intravenous hydrocortisone, which will rapidly improve hyperkalemia in most cases. Identification and treatment of the precipitating cause of the crisis are one of the therapeutic measures. Infections can be treated as identified, according to the local protocols. Within few hours of the commencement of appropriate therapy, adrenal crisis should begin to resolve.[25] However, intensive treatment and monitoring should continue for the next 24–48 h, aiming to commence oral maintenance therapy.

Definitive diagnosis involves tests for serum cortisol, aldosterone, and ACTH concentrations. The point in the setting of adrenal crisis is to treat on suspicion after drawing a paired cortisol and ACTH samples, optional including 21-hydroxylases autoantibodies (for retrospective analysis).[19] The basal concentrations of cortisol and aldosterone are subnormal and fail to increase after ACTH stimulation test. A low normal concentration of serum cortisol in the context of acutely unwell patient is abnormal and does not require ACTH stimulation test. For example, an early morning (08:00 am) serum cortisol concentration lower than 3 μg/dL (80 nmol/l), and a concentration lower than 18 μg/dL (500 nmol/l) after 30 min of administration of 250 μg of intravenous (standard dose) ACTH is diagnostic.[12] In contrast, ACTH is elevated in primary adrenal insufficiency. In addition, 24-h urinary measurements of cortisol metabolite, 17-hydroxycorticosteriod (17-OHCS) excretion is also low. Also known as the tetracosactide (1-24 ACTH) test or Synacthen test has very high sensitivity.[13] It is worthy to note that serum cortisol and ACTH stimulation test may not be reliable in an acutely unwell patient and need to be repeated when the patient is stable. Blood glucose levels and glutamic acid decarboxylase antibodies may aid in early diagnosis of type 1 diabetes mellitus, which may be associated with an autoimmune cause.

The functional state of the thyroid gland is ascertained by TFTs. Thyroid-stimulating hormones and antithyroid antibodies (thyroid peroxidase autoantibody) may be helpful in the diagnosis of patients with hypothyroidism or hyperthyroidism. The clinician should be suspicious of adrenal (combined endocrine) insufficiency in any patient who is diagnosed to be hypothyroid or hyperthyroid.

Plain abdominal radiographs may show calcification of the adrenals seen in tuberculosis. Abdominal ultrasonography and CT-scan of the abdomen may aid in excluding adrenal gland metastasis, tuberculous, or infiltrative lesions. CT-scan of the brain may show evidence of pituitary or hypothalamic lesions. Magnetic resonance imaging reveals reduction in size (shrunken) in the adrenal gland in autoimmune destructive lesions, enlarged adrenals in infections, or evidence of adrenal hemorrhages.

In a seriously unwell patient with an adrenal crisis, a tissue biopsy may show evidence of malignancy, sarcoidosis, or infiltrative lesions. However, tissue biopsy may be less relevant as emergency treatment should not wait for these investigations or their results. A culture of tissue extracts may reveal acid-fast bacilli in tuberculous adrenalitis, as in the index case of the patient.

Admit the patient into the intensive care unit or high-dependence unit for appropriate monitoring and management.

What are the long-term care options in the prevention of adrenal crisis?

There are no universal guidelines for steroid supplementation in terms of appropriate dosing in patients with increased steroid demand during intercurrent illnesses or stressor such as surgery, burns, trauma, or infections.[13]

Several points require to be considered in addressing long-term care in patients with adrenal crisis. Depending on the degree of demand and challenge severity, patients need optimization of their steroid therapy. Cortisone acetate is a treatment option; however, prednisolone is only recommended in certain conditions. During periods of increased cortisol demand as a result of the stress of medical and surgical conditions, appropriate dose-adjustments should be carried out.[22] Doses of cortisol in excess of 300 mg per day may not be beneficial and/or have unwarranted risks of precipitating

Cushing's syndrome. These patients will continue to require daily replacement of aldosterone by the administration of fludrocortisone (0.05–0.3 mg) orally. However, patients should be warned of the potential complications of stopping their glucocorticoid therapy and inform treating clinicians of the need for increased steroid therapy during illness or surgery.

In patients with adrenal insufficiency who are admitted as in-patients for certain procedures or surgery, steroids must not be delayed or withheld to avert irreversible acute cardiovascular collapse, hypovolemia, hypotension, and circulatory shock.

Patients' education should be aimed at preventive strategies and symptom recognition, particularly in those with a background Addison's disease. Education is vital in the prevention of adrenal crisis.[24,25] Self-injection techniques should be integrated into patients' education strategies. Patients should carry their self-injection hydrocortisone emergency kits. Patients are expected to carry a bracelet or tag or identifier card of possible hypoglycemia and possible sudden death if steroid therapy is not instituted if in crisis, which should alert the triage personnel whenever they present in ED. A European emergency steroid card has been implemented in many European countries, and this is life-saving.[26,27] As the time between the presentation of card and initiation of corticosteroid administration can be reduced, therefore improving management.[8]

Endocrine nurses, anesthetists, surgeons, physicians, and GPs also play important roles in both patients' training and in early recognition and referral to avert this potentially lethal condition. The strategy introduced by the *British Medical Journal* in championing patient partnership with their involvement in co-producing articles and papers plays an essential role in the improvement of the quality, safety, and sustainability of healthcare.

The frequency of adrenal crisis can be reduced by annual influenza vaccinations of patients with adrenal insufficiency. In addition to annual endocrinology clinic follow-ups and reviews, patients should be encouraged to join a Patient Support Group such as the UK Addison's Disease Support Group (http://www.addisons.org.uk/).

Conclusion

Adrenal crisis is an uncommon but acute life-threatening medical emergency. A high index of suspicion is paramount in the clinical diagnosis of adrenal crisis in patients who may present with vomiting, refractory hypotension, hyponatremia, hypoglycemia, and circulatory shock, more importantly, in those with a history of adrenal insufficiency. Patients with known Addison disease should be identified early to increase their glucocorticoid therapy in addition to fluids, particularly during intercurrent illnesses, trauma, or surgery. The case under discussion presented an acute stage, so an early admission and transfer to acute medical units was vital to adequate treatment and fluid monitoring to avoid the potential life-threatening shock that may ensue.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. White K, Arlt W. Adrenal crisis in treated Addison's disease: A predictable but under-managed event. Eur J Endocrinol 2010;162:115-20.
2. Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M, *et al*. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. Eur J Endocrinol 2012;167:35-42.
3. Burman P, Mattsson AF, Johannsson G, Höybye C, Holmer H, Dahlqvist P, *et al*. Deaths among adult patients with hypopituitarism: Hypocortisolism during acute stress, and *de novo* malignant brain tumors contribute to an increased mortality. J Clin Endocrinol Metab 2013;98:1466-75.
4. Bergthorsdottir R, Leonsson-Zachrisson M, Odén A, Johannsson G. Premature mortality in patients with Addison's disease: A population-based study. J Clin Endocrinol Metab 2006;91:4849-53.
5. Bensing S, Brandt L, Tabaroj F, Sjöberg O, Nilsson B, Ekbom A, *et al*. Increased death risk and altered cancer incidence pattern in patients with isolated or combined autoimmune primary adrenocortical insufficiency. Clin Endocrinol (Oxf) 2008;69:697-704.
6. White K, Wass J. Emergencies R us: More from our 2013 survey. Newsletter 2014;115:3-5.
7. Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: Increased risk with age and in those with bacterial infections. BMC Endocr Disord 2014;14:79.
8. Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the management of adrenal crisis – Targets, limits and reality. Clin Endocrinol (Oxf) 2015;82:497-502.
9. Meyer G, Neumann K, Badenhoop K, Linder R. Increasing prevalence of Addison's disease in German females: Health insurance data 2008-2012. Eur J Endocrinol 2014;170:367-73.
10. Erichsen MM, Løvås K, Fougner KJ, Svartberg J, Hauge ER, Bollerslev J, *et al*. Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death. Eur J Endocrinol 2009;160:233-7.
11. Zelissen PM. Addison Patients in the Netherlands: Medical Report of the Survey. The Hague, The Netherlands: Dutch Addison Society; 1994.
12. Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, *et al*. Epidemiology of adrenal crisis in chronic adrenal insufficiency: The need for new prevention strategies. Eur J Endocrinol 2010;162:597-602.
13. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-93.
14. Nieman LK, Chanco Turner ML. Addison's disease. Clin Dermatol 2006;24:276-80.
15. Jacobs TP, Whitlock RT, Edsall J, Holub DA. Addisonian crisis while taking high-dose glucocorticoids. An unusual presentation of primary adrenal failure in two patients with underlying inflammatory diseases. JAMA 1988;260:2082-4.
16. Cronin CC, Callaghan N, Kearney PJ, Murnaghan DJ, Shanahan F. Addison disease in patients treated with glucocorticoid therapy. Arch Intern Med 1997;157:456-8.

17. Shaikh MG, Lewis P, Kirk JM. Thyroxine unmasks Addison's disease. Acta Paediatr 2004;93:1663-5.
18. Ten S, New M, Maclaren N. Clinical review 130: Addison's disease 2001. J Clin Endocrinol Metab 2001;86:2909-22.
19. Lundy JB, Slane ML, Frizzi JD. Acute adrenal insufficiency after a single dose of etomidate. J Intensive Care Med 2007;22:111-7.
20. Sarver RG, Dalkin BL, Ahmann FR. Ketoconazole-induced adrenal crisis in a patient with metastatic prostatic adenocarcinoma: Case report and review of the literature. Urology 1997;49:781-5.
21. Khosla S, Wolfson JS, Demerjian Z, Godine JE. Adrenal crisis in the setting of high-dose ketoconazole therapy. Arch Intern Med 1989;149:802-4.
22. Coursin DB, Wood KE. Corticosteroid supplementation for adrenal insufficiency. JAMA 2002;287:236-40.
23. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: Limitations of current assessment methods. J Clin Endocrinol Metab 2006;91:3725-45.
24. Graves L 3rd, Klein RM, Walling AD. Addisonian crisis precipitated by thyroxine therapy: A complication of type 2 autoimmune polyglandular syndrome. South Med J 2003;96:824-7.
25. Papierska L, Rabijewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. Int J Endocrinol 2013;2013:482370.
26. Lee MT, Won JG, Lee TI, Yang HJ, Lin HD, Tang KT. The relationship between morning serum cortisol and the short ACTH test in the evaluation of adrenal insufficiency. Zhonghua Yi Xue Za Zhi (Taipei) 2002;65:580-7.
27. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003;139:194-204.