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Agnieszka Ciastkowska-Berlikowska¹, Dariusz Zawadzki²

Adrenal crisis as a life-threatening condition

Przełom nadnerczowy jako stan zagrożenia życia

¹ Department of Emergency Medicine, Military Medical Academy Memorial Teaching Hospital – Central Veterans' Hospital, ORCID: 0000-0003-3469-6766, Łódź, Poland

² Department of Paediatric Emergency Medicine, II Department of Paediatrics, Medical University of Lodz, ORCID: 0000-0003-4560-0440, Łódź, Poland

Correspondence: Agnieszka Ciastkowska-Berlikowska, Department of Emergency Medicine, Military Medical Academy Memorial Teaching Hospital – Central Veterans' Hospital, Żeromskiego 113, 90-549 Łódź, Poland, tel.: +48 42 639 34 20

Abstract

Adrenal crisis is a medical emergency, which requires quick, accurate diagnosis and the implementation of adequate treatment. It usually occurs in patients taking glucocorticoid therapy due to chronic adrenal insufficiency in conditions that demand increased glucocorticoids, such as infection, trauma, surgery, myocardial infarction, stroke, exercise or acute stress. The disease follows a course of shock that does not respond to catecholamines. Prodromal symptoms include decreased appetite, nausea, vomiting, abdominal pain, joint or muscle pain, and fatigue. This is followed by fluctuating consciousness, as well as reduced blood pressure and tachycardia, which are symptoms of shock. These symptoms result from the following metabolic disorders: hyponatremia, hyperkalemia, hypoglycaemia and mild hypercalcemia. Due to the absence of characteristic symptoms in adrenal crisis, the basis for correct diagnosis in a prehospital setting is a carefully collected medical history, followed by a detailed physical examination that should pay particular attention to discoloration of the skin (so-called *melasma suprarenale*) that is not exposed to light: the hands (especially creases), elbows, areolae, scars and buccal mucosa, which is one of the symptoms of primary adrenal insufficiency (Addison's disease). The therapeutic approach consists in the administration of intravenous hydrocortisone (to moderate cortisol deficiency), modifying fluid and electrolyte imbalances and abnormalities of acid-base balance, and treating the disease that has led to decompensation of the patient's clinical condition, which in many cases is an infection. Adrenal crisis left untreated leads to patient death.

Keywords: adrenal crisis, acute adrenal insufficiency, glucocorticoids

Streszczenie

Przełom nadnerczowy jest stanem zagrożenia życia. Wymaga ustalenia szybkiego, trafnego rozpoznania oraz wdrożenia adekwatnego leczenia. Najczęściej rozwija się u chorych leczonych glikokortykosteroidami z powodu przewlekłej niedoczynności kory nadnerczy w stanach zwiększonego na nie zapotrzebowania, takich jak: infekcja, uraz, zabieg chirurgiczny, zawał serca, udar mózgu, wysiłek fizyczny czy silny stres. Choroba przebiega pod postacią wstrząsu, który nie reaguje na działanie katecholamin. Objawy prodromalne obejmują: obniżone łaknienie, nudności, wymioty, bóle brzucha, bóle mięśni i stawów oraz osłabienie. Następnie dochodzi do zaburzeń świadomości, a także obniżenia ciśnienia tętniczego i tachykardii, które są objawami wstrząsu. Wymienione objawy stanowią skutek następujących zaburzeń metabolicznych: hiponatremii, hiperkalemii, hipoglikemii i łagodnej hiperkalcemii. Ze względu na brak charakterystycznych objawów przełomu nadnerczowego podstawą prawidłowego rozpoznania w warunkach przedszpitalnych jest wnikliwie zebrany wywiad, a następnie szczegółowe badanie przedmiotowe, w którym szczególną uwagę trzeba zwrócić na przebarwienia skóry (tzw. *melasma suprarenale*) nieekspozowanej na światło: dłoni (w szczególności bruzd), łokci, otoczek sutkowych, blizn oraz błony śluzowej policzków, będące jednym z objawów pierwotnej niedoczynności kory nadnerczy (choroba Addisona). Postępowanie polega na podawaniu hydrokortyzonu dożylnie (w celu uzupełnienia niedoboru kortyzolu), modyfikowaniu zaburzeń wodno-elektrolitowych i kwasowo-zasadowych, a także leczeniu choroby, która spowodowała dekompensację stanu klinicznego pacjenta, przy czym w wielu przypadkach jest to infekcja. Nieleczony przełom nadnerczowy prowadzi do zgonu chorego.

Słowa kluczowe: przełom nadnerczowy, ostra niewydolność kory nadnerczy, glikokortykosteroidy

INTRODUCTION – THE ANATOMY AND PHYSIOLOGY OF THE ADRENAL CORTEX

The adrenal glands are paired endocrine glands located on top of both kidneys. They are composed of two parts – the outer, called the cortex, and the inner – the medulla⁽¹⁾.

The adrenal cortex is responsible for releasing three classes of hormones: glucocorticosteroids (GCs), mineralocorticosteroids (MCs) and androgens. GCs include cortisol and cortisone, MCs are aldosterone and deoxycorticosterone, while androgens secreted by the adrenal glands are mainly dehydroepiandrosterone (DHEA), androstenedione and testosterone, i.e. sex hormones. The adrenal medulla produces adrenaline and norepinephrine⁽²⁾.

Glucocorticosteroids have a major effect on the function of most organs. They regulate expression of adrenergic receptors in the cardiovascular system and increase the contractile reactivity of myocytes in blood vessels, enhancing the effects of adrenaline and noradrenaline on blood vessels. They also stimulate cardiac contractile force (positive inotropic effect). In the central nervous system, by stabilising cell membranes, they are responsible for the correct water content in cell compartments – they have a beneficial impact on cognitive functioning and the ability to concentrate. In the kidneys, GCs increase glomerular filtration and the excretion patterns of potassium, calcium and phosphates. In the digestive tract, excess cortisol levels delay the rate of renewal of the mucosal lining of the stomach, which reduces its resistance to harmful factors, especially excess hydrochloric acid. They also reduce the production of protective mucus⁽³⁾.

Glucocorticosteroids are commonly used in medicine. Synthesised derivatives of cortisol with a slightly modified chemical structure increase the glucocorticoid effect and reduce sodium and water retention in the body. Glucocorticosteroids obtained in this way, to a lesser extent than natural ones, cause swelling, but exhibit an increased catabolic effect (they cause muscle and skin atrophy, stretch marks, osteoporosis, haemorrhagic diathesis). Only GCs with the 11-OH group (hydrocortisone, methylprednisolone, prednisolone, dexamethasone, ciclesonide, triamcinolone) cause biological effects in the body. Synthesised cortisol derivatives, administered in supraphysiological doses, have a wide range of applications, mainly due to their anti-inflammatory and immunosuppressive effects⁽³⁾.

DEFINITION

Adrenal crisis is a set of clinical symptoms caused by a significant, sudden lack of cortisol, which poses a direct threat to the patient's life. In the case of the necessity of GC supplementation, it is the result of a relative or absolute deficiency of this hormone, secondary to the imbalance between the increased demand for hydrocortisone and an insufficient increase in its dose⁽¹⁾.

Adrenal crisis can occur in:

1. people with undiagnosed adrenal insufficiency as a prodromal condition;
2. patients with diagnosed and treated adrenal insufficiency:
 - a) after discontinuation of substitution treatment,
 - b) in stressful situations, without modification of hydrocortisone dosage or as a result of insufficient absorption of hydrocortisone due to diarrhoea or vomiting,
 - c) in the case of increased GCs metabolism under the influence of concurrent pharmacotherapy or in hyperthyroidism;
3. patients with previously normal secretory function of the adrenal glands:
 - a) arising from damage to previously healthy adrenal glands by: trauma, haemorrhage in the course of disseminated intravascular coagulation, anticoagulation therapy or pregnancy eclampsia,
 - b) in the critical phase of severe diseases, due to dysfunction of the hypothalamic–pituitary–adrenal axis in combination with tissue resistance to GCs and excessive inflammatory response⁽¹⁾.

Patients with chronic adrenal insufficiency, either primary or secondary, are the most vulnerable group to adrenal crisis. These patients may experience adrenal crisis in a stressful situation, in the absence of a cover with a sufficient dose of hydrocortisone. Sometimes it is the first symptom of disease. For this reason, clinical examination, which should include data on comorbidities, family medical history, medications, past surgical history, as well as prodromal symptoms, including weakness with tendency to periodic fainting (as a result of orthostatic hypotension or hypoglycaemia), fatigability and muscle weakness, reduced exercise tolerance during physical work and stressful situations, weight loss, decreased appetite, nausea, salt craving, loose stools, and joint or muscle pain, is the most important element of diagnosis⁽¹⁾.

The prevalence of primary adrenocortical insufficiency (Addison's disease) is between 40 and 110 per million in the Caucasian population. The disease most often presents during the second or third decade of life, and is much more common in women⁽⁴⁾. Addison's disease is a set of clinical symptoms caused by long-term deficiency of adrenal cortex hormones, mainly cortisol, as a result of direct damage to the adrenal glands. Autoimmunity is the most common cause (70–90% of cases). Primary adrenal insufficiency may be accompanied by other autoimmune diseases, most often of the thyroid gland (polyglandular syndromes). Other causes of Addison's disease include tuberculosis, other infectious diseases (mycoses, acquired immunodeficiency syndrome – AIDS), neoplasms (metastases and primary neoplasms), metabolic disorders (amyloidosis, haemochromatosis, adrenoleukodystrophy, adrenomyeloneuropathy), congenital dysfunctions (congenital adrenal hyperplasia, adrenocorticotrophic hormone – ACTH, Allgrove's syndrome, adrenal hypoplasia), drug-induced reduction in the adrenocortical hormone formation, status

post bilateral adrenalectomy, status post haemorrhage into both adrenal glands, and granulomatous infiltration (sarcoidosis)⁽⁵⁾. Clinical symptoms include skin discoloration, especially in areas exposed to sunlight, with brown colour of the elbows, flexion creases on the palms and back of the hands, areola and scars, as well as, in some cases, brown spots on the oral mucosa (changes resulting from the excess of ACTH and melanotropin due to their insufficient feedback inhibition by cortisol), low blood pressure and orthostatic hypotension⁽⁵⁾.

Secondary adrenal insufficiency is reported with a frequency between 150 and 280 per million, and is more common in women⁽⁴⁾. It is a set of clinical symptoms caused by a long-term deficit of adrenal cortex hormones due to ACTH deficiency. The most frequent causes are: feedback inhibition of ACTH secretion as a result of chronic corticotherapy, the consequences of surgical interventions in pituitary and parasellar tumours, and autoimmunity. Other causes include previous pituitary apoplexy, postpartum hypopituitarism, as well as infiltrative and post-traumatic changes. The clinical symptoms do not differ from those of primary adrenal insufficiency⁽⁵⁾.

According to the literature, symptoms of gastrointestinal tract infection (diarrhoea, vomiting) are the most common factor which causes acute adrenal insufficiency in adults. The scientific literature shows that these symptoms account for approximately 33–59% of cases of adrenal crisis^(6,7). However, they also represent symptoms of acute adrenal insufficiency, which may lead to overestimating their frequency as triggers⁽⁸⁾. Acute bacterial and viral infections (infectious lung diseases, urinary tract infections, sepsis, influenza-like syndrome) are the second most common (17–24%) cause. In a prospective study by Hahner et al. conducted in a group of 423 patients (2-year follow-up), the triggering factor was severe occupational or personal stress in 30% of cases among 46 patients with acute adrenal insufficiency (frequency similar to that of an infectious cause). Other factors were surgeries, severe pain, trauma, childbirth, intense prolonged exercise, and heat⁽⁹⁾. In some studies, approximately 11% of crises were caused by repeated discontinuation of hydrocortisone treatment⁽⁷⁾. Other causes of acute adrenal insufficiency in the aforementioned studies were introduction of long-term use of diuretics, low-sodium diet or chemotherapy causing gastrointestinal ailments, no dose adjustment for hydrocortisone after the introduction of treatment, which may affect its metabolism (phenytoin, carbamazepine, rifampicin, mitotane, resins, exenatides). The cause was not identified in 1–7% of reported cases⁽⁷⁾.

CLINICAL SYMPTOMS

The clinical symptoms in adrenal crisis are non-specific and some of them are the same as the triggering factor^(10–14). They usually appear within a few hours. The median time between the onset of the first symptoms and full-symptom crisis is approximately 24 hours⁽¹⁵⁾.

The clinical picture of the disease includes:

- 1. prodromal symptoms:** loss of appetite, nausea, muscle pain and malaise;
- 2. symptoms of upcoming crisis:** progressing weakness, influenza-like muscle pain, abdominal pain, nausea, gradual drop in blood pressure, possible increase in body temperature caused by cytokines released in cortisol deficiency;
- 3. symptoms of crisis:** severe weakness, fluctuating consciousness, vomiting, diarrhoea, low blood pressure and tachycardia, distributional shock, also known as vascular shock⁽¹⁾.

In adrenal crises caused by disseminated intravascular coagulation in the course of sepsis (especially meningococcal sepsis), symptoms of acute adrenal insufficiency are accompanied by dermal haemorrhages (Waterhouse–Friderichsen syndrome). In patients in the critical phase of severe disease, a drop in blood pressure that cannot be compensated by parenteral administration of fluids and vasopressors is the main symptom⁽¹⁾.

DIAGNOSIS

Due to the lack of characteristic disease symptoms, a detailed medical history provides an opportunity to establish proper diagnosis in the prehospital setting. On physical examination, attention should be paid to discoloration of the skin (so-called melasma suprarenale) that is not exposed to light, i.e., the hands (especially creases), elbows, areola, scars and buccal mucosa, which is one of the symptoms of primary adrenal insufficiency (Addison's disease)⁽¹⁶⁾.

Symptoms suggestive of acute adrenal insufficiency include hypotension which is refractory to emergency treatment with drugs elevating arterial blood pressure (fluid therapy and vasopressors) and hypoglycaemia⁽¹⁾.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis should include acute myocardial infarction, pulmonary embolism, acute appendicitis, cholecystolithiasis, acute pancreatitis, internal or external bleeding, perforation of gastric or duodenal ulcer, sepsis⁽¹⁾.

PREHOSPITAL APPROACH

The aim of prehospital treatment is to establish a diagnosis as quickly as possible. The intention is to reduce the risk of acute complications and patient death. Next, the proceedings should include the following actions:

1. Protection of vital functions according to the ABCDE scheme (A – airway, B – breathing, C – circulation, D – disability, E – exposure).
2. Intravenous administration of 100 mg hydrocortisone.
3. In case of hypotension (systolic blood pressure <90 mm Hg), initiation of fluid therapy – replenishment of fluid with 0.9% NaCl + 5% glucose solution (in case of hypoglycaemia – 10% solution).

4. In the case of low blood pressure, the use of vasopressor drugs [in type P (primary) emergency medical teams – adrenaline, in type S (specialist) teams – noradrenaline, adrenaline, dobutamine, dopamine]:
 - a) If there is a sustained hypotension despite fluid infusion, continuous intravenous catecholamine infusion should be administered to contract the vessels. The normal procedure is to start with the administration of norepinephrine at a dose of 1–20 µg/min (max. 1–2 µg/kg/min). Adrenaline at a dose of 0.05–0.5 µg/kg/min or dopamine at a dose of 3–30 µg/kg/min may be considered.
 - b) In patients with low cardiac output despite adequate hydration (or hyperhydration), administration of dobutamine at a dose of 2–20 µg/kg/min.
5. An attempt to identify and treat the disease that could be a potential cause of decompensation of the patient's clinical condition and the occurrence of acute adrenal insufficiency⁽⁵⁾.

EARLY HOSPITAL TREATMENT

The treatment is aimed at correcting cortisol, fluid and glucose deficiencies, fixing electrolyte disturbances, and simultaneously controlling possible infection and the underlying disease triggering adrenal crisis. The primary elements of therapy include treatment of acute adrenal insufficiency – immediately after the collection of blood samples for basic (glucose, sodium, potassium, creatinine) and hormonal tests (cortisol, ACTH) and possibly for infection:

1. hydrocortisone – i.v. injection 100 mg, then 100 mg i.v. infusion every 6 hours, and after normalisation of blood pressure and heart rate – 50 mg i.v. or i.m. every 6 hours;
2. 2,000–3,000 mL 0.9% NaCl + 5% glucose solution (10% solution in case of hypoglycaemia) and blood substitutes, e.g. dextran, plasma or albumin solution to correct hypovolaemia; initially 1 L/h, in total 2–4 L in 24 hours;
3. treatment of hyponatremia – 3.5–10.0 g within 24 hours;
4. low-molecular-weight heparin in a prophylactic dose.

Continuous efforts are also needed to monitor the patient's condition – the amount and type of infused fluids and the dose of sodium chloride should depend on fluid balance, severity of electrolyte disturbances, as well as cardiovascular and renal function⁽¹⁾.

PROGNOSIS

According to the literature, adrenal crisis is the cause of death in patients with adrenal insufficiency in 6–15% of cases^(17–19). In the study by Hahner et al., mortality in acute adrenal insufficiency was 0.5/100 patients/year⁽⁹⁾. The risk factors reported in retrospective studies were primary adrenal insufficiency, female gender, comorbidities (asthma, diabetes) and diabetes insipidus^(7,8,20).

Conflict of Interest

The authors have no financial or personal connections to declare with other persons or organisations that could adversely affect the content of the publication and claim the right to this publication.

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