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Adrenal Crisis In A Patient With An Adrenal Tumor

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ABSTRACT

Sudden and dangerous hormone deficiency from the adrenal glands can lead to a critical medical emergency known as adrenal crisis, which may result from adrenal tumors. This case report presents a 63-year-old woman diagnosed with an adrenal crisis due to Addison's disease secondary to an adrenal tumor. The patient experienced progressive weakness, nausea, vomiting, and significant electrolyte imbalances, particularly severe hyponatremia (104 mmol/L). Laboratory findings showed low morning serum cortisol levels (16.5 ng/mL) and elevated ACTH levels (152.7 pg/mL), confirming primary adrenal insufficiency. Imaging revealed bilateral adrenal masses, suggesting hyperplasia or adenoma. The patient was treated with intravenous hydrocortisone, fluid resuscitation, and electrolyte correction, which resulted in clinical improvement. She was later transitioned to oral hydrocortisone and scheduled for adrenalectomy. Based on this case report, diagnosing adrenal insufficiency is difficult due to its vague symptoms, often leading to delayed recognition and increased risk of death. Prompt recognition and management of adrenal crisis is critical for better patient survival.

Keywords: *adrenal crisis, Addison's disease, adrenal tumor*

1. INTRODUCTION

Primary adrenal insufficiency, better known as Addison's disease, occurs when the adrenal glands are unable to produce sufficient amounts of glucocorticoid and mineralocorticoid hormones. This condition causes disruptions in various bodily functions, as these hormones play an important role in regulating metabolism, electrolyte balance, as well as the body's response to stress. The imbalance in hormone production due to primary adrenal insufficiency leads to disruption of the negative feedback mechanism to the pituitary gland. As a result, the body responds by increasing the production of adrenocorticotropic hormone (ACTH) in an attempt to stimulate the malfunctioning adrenal glands. This increase in ACTH levels is the hallmark that distinguishes primary adrenal insufficiency from the secondary form, where the disruption occurs in the pituitary gland or hypothalamus, rather than the adrenal glands themselves.

Although classified as a rare disease with a prevalence of 35-140 cases per million population and an annual incidence of 4 cases per million in the Caucasian population, this condition requires serious attention because of its potential life-threatening complications. The most common cause of primary adrenal insufficiency in Western countries is autoimmune adrenalitis, responsible for approximately 90% of cases. This can occur by itself or as part of a larger group of autoimmune disorders. Other causes include infection, genetic disorders, malignancy, use of certain medications, and critical conditions. The challenge in diagnosing this disease lies in its clinical manifestations which are often non-specific, resulting in delays in diagnosis (Regan *et al.*, 2019). Adrenal hormones play a vital role in body homeostasis, including the regulation of energy, electrolytes, and fluids. When an acute adrenal crisis occurs, the patient can experience shock and severe hypotension which can be fatal if not treated immediately. An in-depth understanding of this condition is very important for early diagnosis and appropriate management, considering the potential for serious complications that can arise. To increase awareness of this disease, in this case report we will present the case of a 63 year old woman who experienced an adrenal crisis due to Addison's Disease due to an adrenal tumor.

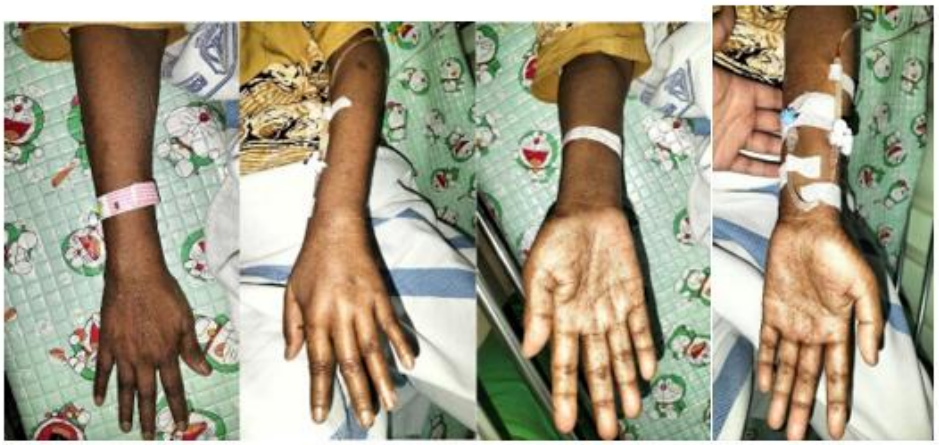
Case Report

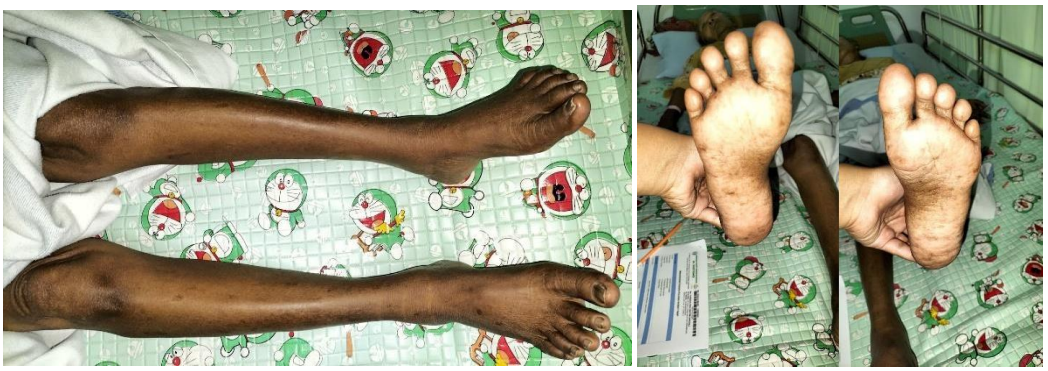
A 63-year-old woman, Javanese, lives in Surabaya, works as a married housewife, has 3 children. The patient came to the Internal Medicine Endocrine Clinic with the main complaint of weakness for the previous 3 days. The patient also complained that his body felt stiff and his legs were weak so he couldn't stand for long. The patient also complained of heartburn since 3

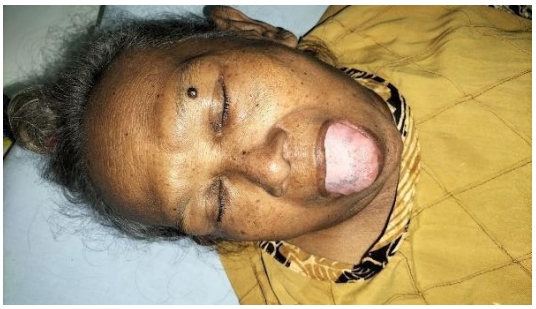
days ago accompanied by nausea and vomiting containing food. While at home the patient only wanted to eat porridge but 1 day ago every time he ate porridge he vomited. Complained of decreased appetite since the last 1 week. Another complaint was cough with no phlegm since the last 3 days, no fever, shortness of breath and chest pain. The patient admitted that his bowel movements were normal, there was no diarrhea and his BAK was within normal limits. The patient admitted that he did not notice the change in skin color becoming darker throughout the body because it was considered genetically normal. The patient has a history of diabetes mellitus for the last 10 years with routine medication Acarbose 2x50 mg and gliquidone 1x30 mg. history of hypertension since the last 10 years with routine medication Amlodipine 1x10 mg.

The patient had a history of being hospitalized 5 months ago at Dr Soetomo Hospital Surabaya with complaints of weakness, then a diagnosis of recurrent hypoglycemia and severe hyponatremia (116), after treatment for 5 days, the complaints improved and the patient had routine control. During the 5-month control period the patient's sodium levels tended to decrease, blood pressure was unstable, sugar levels were never high. Recent treatment history from the Internal Medicine Polyclinic, namely 3x1 salt capsules, 3x15ml sucralfate, 1x20 mg omeprazole and 3x1 domperidone.

From the physical examination while in the treatment room, blood pressure was 86/59 mmHg, pulse 105 times per minute, respiration rate 20 times per minute, temperature afebrile, oxygen saturation 99% without additional oxygen. From the general physical examination, hyperpigmentation was found on the tongue, both hands and both feet. The results of other physical examinations showed no abnormalities.



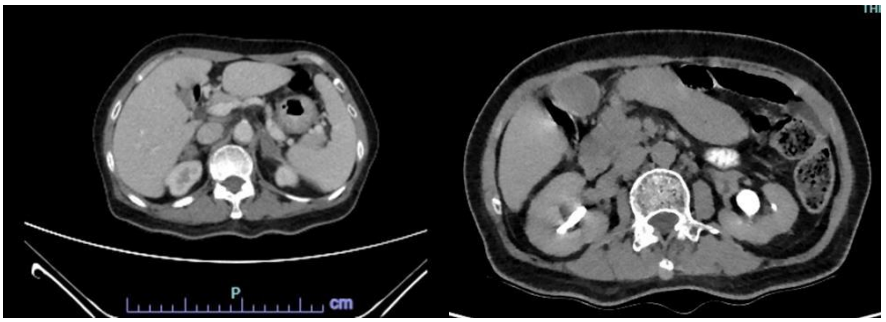


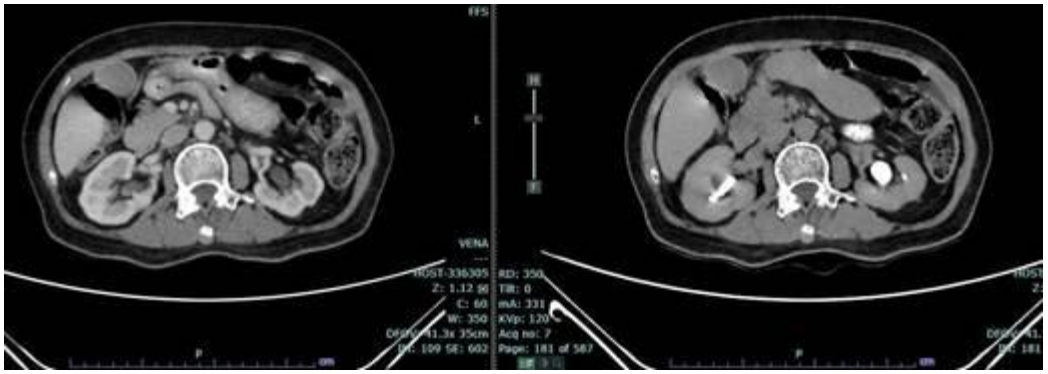


From the results of the initial supporting examination, the hemoglobin level was 12.3 gr/dL, the leukocyte count was 7.29 x 10^3 µL, platelets 150,000 µL, blood sugar level 77 mg/dL. Liver function, albumin and kidney function were normal. Low

sodium levels of 104 mmol/L, and normal potassium 5 mmol/L. The results of urinalysis were normal and urine culture found no microorganisms. The patient found a normal TSH level of 0.9200 µIU/mL, a decrease in morning serum cortisol level (09.00) of 16.5 ng/mL (45.5 - 208.2 ng/mL) and an increase in ACTH level of 152.7 pg/mL (7.4 - 64.3 pg/mL). From photo inspection

The thorax does not appear abnormal. Abdominal CT scan with contrast showed a solid mass (39 HU), clear boundaries, regular edges, size +/- 2.6 x 1.1 x 3.3 cm in the right adrenal and +/- 2.9 x 1.3 x 2.9 cm in the left adrenal, which did not show abnormal contrast enhancement (40 HU), the lesion in the adrenal was attached to the inferior wall of the liver with clear boundaries, the lesion in the left adrenal was attached to the inferior wall of the spleen with clear boundaries with the conclusion of a non-enhancing solid mass in the right and left adrenal. can be a differential diagnosis: 1. Adrenal hyperplasia; 2. Adrenal adenoma.





The patient was diagnosed with adrenal crisis with *Addison disease* ec adrenal tumor, type 2 DM, hyponatremia (104) hypotonic hypovolemic. The patient was given infusion therapy of 3% NaCl 500 ml and Nacl 0.9% 1,000 ml in 24 hours, metoclopramide 3x10 mg IV injection, with oral therapy sucralfate 3x15 ml, N-acetylcysteine 3x200mg and 3x1 salt capsule. The patient was given an intravenous injection of 3x100 mg hydrocortisone for 3 days then reduced to 2x50 mg intravenously. There was no increase in blood sugar levels during hydrocortisone administration. During the treatment period the patient experienced clinical improvement, appetite improved, complaints of weakness decreased, independent mobilization, no complaints of defecation, no fever, no shortness of breath. Laboratory results evaluating treatment on the 3rd day showed a decrease in potassium levels (3.2). The patient was given 3x1 oral potassium tablet therapy for 2 days then the potassium levels returned to normal.

After administering intravenous hydrocortisone for 7 days and normal laboratory evaluation results, the patient was sent home with a plan for adrenalectomy at the polyclinic. Steroid administration was changed to an oral preparation of hydrocortisone 20 mg in the morning and 10 mg in the evening for 1 month and during the evaluation the patient experienced clinical improvement, electrolyte levels were normal and cortisol levels increased to 189 ng/mL.

2. RESULT AND DISCUSSION

Addison's disease, or primary adrenal insufficiency, stems from direct damage to the adrenal glands, leading to deficiencies in crucial hormones produced by its various layers: mineralocorticoids, glucocorticoids, and sex hormones (Bornstein *et al.*, 2016b). This condition has the potential to cause acute decompensation and adrenal crisis which can be fatal (Chantzichristos *et al.*, 2017; Lousada, Mendonca and Bachega, 2021; Ngaosuwan *et al.*, 2021). This condition is quite rare due to delays in diagnosis due to several main factors. First, the symptoms that appear are often non-specific and develop slowly, such as fatigue, loss of appetite, weight loss, nausea, vomiting and abdominal pain which are often mistaken for gastrointestinal or psychiatric illnesses (Bleicken *et al.*, 2010). Second, the lack of knowledge of medical personnel about this disease causes 67% of patients to consult at least 3 doctors before getting the right diagnosis, and 68% of patients initially get the wrong

diagnosis (Bleicken *et al.*, 2010). Third, more specific symptoms such as hypotension (55%) and skin hyperpigmentation (41%) appear less frequently, so they do not trigger suspicion of adrenal insufficiency (Papierska and Rabijewski, 2013). Fourth, hyponatremia, which is an important diagnostic clue, is often overlooked - in one study it was found that 57% of patients had hyponatremia for at least 3 months before the diagnosis was made but were not followed up with adrenal function tests (Papierska and Rabijewski, 2013). Delay in diagnosis can increase the risk of mortality according to the results of a retrospective cohort study in England involving 6,821 adrenal insufficiency patients (2,052 primary; 3,948 secondary) compared with 67,564 controls in the period 1987 to 2017 where the death rate was higher in patients than controls (35.2 vs 21.0 per 1,000 person-years), the risk of death was higher in primary adrenal infusion (HR). 1.83) compared to secondary adrenal insufficiency (HR 1.52) and the highest risk occurs in the first year after diagnosis and adrenal crisis contributes to 10% of deaths (Ngaosuwan *et al.*, 2021).

Many of the symptoms of primary adrenal insufficiency are non-specific and can mimic adrenal insufficiency due to various other causes. They include fatigue, nausea, loss of appetite, pain in the abdomen, joints and muscles, and weight loss. In addition, patients may experience low blood pressure, decreased blood volume that causes dizziness when standing, and electrolyte imbalances such as low sodium levels (hyponatremia) and low blood sugar (hypoglycemia) without an apparent cause (Bancos *et al.*, 2015; Lee *et al.*, 2023). Patients complained of weakness in the body and legs, nausea, vomiting, decreased appetite, heartburn and cough without phlegm. The symptoms of primary adrenal insufficiency can range from mild to life-threatening, and can often go unnoticed until the body experiences serious stress or illness (Betterle, Presotto and Furmaniak, 2019; Hahner *et al.*, 2021). Hyperpigmentation on the tongue, hands and feet is a classic sign of Addison's disease due to increased adrenocorticotropic hormone (ACTH) indicating primary adrenal insufficiency, but the severity of hyperpigmentation varies greatly between individuals. Aldosterone plays a role in regulating sodium and body fluid balance by promoting sodium reabsorption in the kidneys. When aldosterone production decreases, the body loses sodium through urine, leading to decreased blood volume (hypovolemia) and low blood pressure (hypotension). Meanwhile, cortisol normally provides negative feedback to the hypothalamus and pituitary gland to regulate ACTH production. In Addison's disease, cortisol production is reduced, so this feedback mechanism is disrupted. As a result, the pituitary gland increases the production of POMC, which is a precursor of ACTH and α-MSH. This increase in α-MSH levels contributes to the skin hyperpigmentation typical in Addison's disease, as α-MSH stimulates melanin production by melanocytes. Elevated α-MSH levels trigger skin hyperpigmentation by stimulating melanocortin receptor 1 (MSHR). Apart from appearing in areas that are frequently exposed to sunlight, pigmentation is also more visible in areas with higher friction or mechanical stress. This is due to increased melanocyte activity in those areas in response to mechanical and hormonal stimuli. The appearance of hyperpigmentation on the oral mucosa and scars is a characteristic sign of Addison's disease that distinguishes it from other causes of hyperpigmentation (Hahner *et al.*, 2021; Bondagji *et al.*, 2023). Low blood pressure that worsens on standing (orthostatic hypotension) and an excessive craving for salt can be indicative of aldosterone deficiency in people with primary adrenal insufficiency. In addition, dehydroepiandrosterone (DHEA) deficiency is often associated with loss or lack of hair growth in the armpits and pubic area, dry and itchy skin, and symptoms such as fatigue and decreased sexual desire, especially in women (Betterle, Presotto and Furmaniak, 2019; Hahner *et al.*, 2021; Husebye *et al.*, 2021).

In distinguishing primary from secondary adrenal insufficiency, there are two key factors that need to be considered, namely the symptoms of aldosterone deficiency in patients with adrenal insufficiency primary patients are more susceptible to experiencing significant hypovolemia and hyperkalemia with the desire to consume salt more frequently, as well as signs of excess adrenocorticotropic hormone (ACTH) which produces a byproduct in the form of melanocyte-stimulating hormone-alpha (α-MSH) which has an effect on pigmentation in the melanocortin 1 receptor in skin and mucosal melanocytes, thus causing skin hyperpigmentation resembling brownish skin due to prolonged sunbathing (Mountjoy, 1994).

The patient had severe hyponatremia (104 mmol/L) and low blood pressure (86/59 mmHg) indicating electrolyte disturbances and hypotension typical of primary adrenal insufficiency. The survey showed that most (84%) people with undiagnosed adrenal insufficiency had hyponatremia, more than half (52%) had elevated TSH levels, and one-third (34%) had hyperkalemia. Therefore, hyponatremia of unknown cause should always trigger suspicion of adrenal insufficiency (Sævik *et al.*, 2018). Follow-up laboratory examination showed the patient's morning serum cortisol level was low (16.5 ng/mL) with increased ACTH levels (152.7 pg/mL; normal 7.4 - 64.3 pg/mL). Further examination for the diagnosis of primary adrenal insufficiency is by measuring cortisol levels, where cortisol levels of less than 3 µg/dL are consistent with adrenal insufficiency and if cortisol levels are above 13-18 µg/dL it indicates that adrenal insufficiency is not occurring. If the results are unclear, a cosyntropin stimulation test is performed, in which 250 µg of cosyntropin is administered intramuscularly or intravenously; If cortisol levels remain low after 30 and 60 minutes, the patient is considered to have adrenal insufficiency, but this examination is not available at Dr Soetomo Hospital. To confirm primary adrenal insufficiency, it is necessary to measure adrenocorticotropic hormone (ACTH) levels together with morning cortisol, where ACTH values more than twice the upper limit of normal support the diagnosis of primary adrenal insufficiency (Bornstein *et al.*, 2016b; Lundholm, Ambalavanan and Rao, 2024a; Øksnes and Husebye, 2024).

The main cause of adrenal insufficiency is damage to the adrenal glands due to autoimmune reactions, which accounts for up to 90% of all cases. Apart from autoimmune factors, various other conditions can also damage the adrenal glands.

Infections such as tuberculosis can cause inflammation and damage to the adrenal tissue. Adrenal hemorrhage due to injury or blood clotting disorders can cause acute adrenal dysfunction. Adrenal infarction, which occurs when the blood supply to the gland is blocked, can also lead to adrenal insufficiency. In some cases, adrenal insufficiency develops as a result of cancer spreading to the adrenal glands (metastasis) or as a result of surgical procedures that require removal of the adrenal glands. In addition, congenital abnormalities such as 21-hydroxylase deficiency which is a disorder in the synthesis of steroid hormones can cause adrenal insufficiency from birth. Subsequently, cases of drug-induced primary adrenal insufficiency have been increasingly reported, with incidence rates increasing significantly. While mitotane and etomidate have long been recognized as causes of adrenal dysfunction, recent drugs for cancer and immune diseases, particularly immune checkpoint inhibitors, have increased the risk of iatrogenic adrenal disease. Identifying adrenal insufficiency in patients undergoing treatment can be difficult, as doctors must distinguish whether the symptoms are from adrenal insufficiency or from an underlying disease. Therefore, careful monitoring is required, especially for patients taking medications that are known to affect adrenal function (Lundholm, Ambalavanan and Rao, 2024b).

Once primary adrenal insufficiency is diagnosed, it is important to investigate the cause. One of the main markers of autoimmune adrenal insufficiency is the presence of autoantibodies to the enzyme 21-hydroxylase, which plays a role in the synthesis of adrenal hormones. If a patient is shown to have these autoantibodies, it is possible that they also have other autoimmune diseases. Therefore, doctors need to perform additional tests to detect and treat autoimmune conditions that may accompany adrenal insufficiency, so that patients can receive more comprehensive treatment. Although 21-hydroxylase autoantibodies are the main indicator of autoimmune adrenal insufficiency, not all patients with autoimmune primary adrenal insufficiency will show a positive result in this test. Therefore, if the autoantibody test result is negative, the doctor needs to look for other possible causes by imaging using a CT scan. In patients with negative autoantibody test results, CT imaging of the adrenal glands is recommended to detect any inflammation or damage, such as bleeding or infiltration due to metastasis from cancer outside the adrenal glands (Bornstein *et al.*, 2016a; Betterle, Presotto and Furmaniak, 2019; Hahner *et al.*, 2021; Husebye *et al.*, 2021). The next examination we carried out was a CT scan of the abdomen to look for masses in the adrenal area. The findings were bilateral solid masses in the right and left adrenals consistent with adrenal hyperplasia or adenoma. Bilateral masses in the right and left adrenals suggest the possibility of hyperplasia or adenoma as a cause of non-autoimmune Addison's disease. Autoimmune causes are less common in Asian populations than in Western countries.

The patient was treated with adrenal crisis therapy in the form of intravenous hydrocortisone with an initial dose of 3x100 mg for 3 days then reduced to 2x50 mg, correction of hyponatremia with infusion of 3% NaCl (500 mL) and 0.9% NaCl (1,000 mL) within 24 hours. Other supportive therapies such as metoclopramide for nausea/vomiting and sucralfate for heartburn. After clinical stabilization during 7 days of treatment, hydrocortisone was switched to oral form (20 mg in the morning and 10 mg in the evening). The patient was planned for elective adrenalectomy. The patient showed clinical improvement after intravenous followed by oral glucocorticoid therapy. Electrolyte evaluation remained normal during control advanced. Adrenalectomy was planned to treat the adrenal mass which was the main etiology of primary adrenal insufficiency in this patient.

Despite slight differences in dosage, all adrenal insufficiency treatment guidelines have the same goals. The various guidelines for the management of adrenal insufficiency, published by medical organizations in the United States, Europe, the United Kingdom, Japan, and other countries, have the same treatment goals of optimizing the dose of glucocorticoids, improving the patient's quality of life, preventing complications due to overdose, and avoiding death from adrenal crisis (Bornstein *et al.*, 2016b; Catch them *et al.*, 2016; Woodcock *et al.*, 2020; Hahner *et al.*, 2021).

Glucocorticoids are released into the blood in a fluctuating pattern throughout the day, peaking in the morning and lowest in the middle of the night. Oral hydrocortisone or cortisone acetate is the standard glucocorticoid treatment, with cortisone acetate requiring conversion in the liver to hydrocortisone before it is active. Hydrocortisone is the primary choice in glucocorticoid replacement therapy for patients with adrenal insufficiency. In the plasma, hydrocortisone has a half-life of about 90 minutes. Therefore, it is administered two to three times a day, with the highest dose given in the morning upon waking. If a two-dose regimen is used, the second dose is given in the afternoon. Meanwhile, in the three-dose regimen, subsequent doses are given at lunch and at night to mimic the body's natural pattern of circadian rhythm (Bornstein *et al.*, 2016a). The recommended starting dose of hydrocortisone is 15 to 25 mg per day, divided into 2 or 3 doses, with a higher dose in the morning (10-15 mg) and lower in the afternoon (5-10 mg) to mimic natural cortisol production patterns. An evening dose (2.5-5 mg) may be considered if the patient experiences symptoms at night (Lundholm, Ambalavanan and Rao, 2024a).

Hydrocortisone is the most commonly used drug for glucocorticoid replacement therapy due to its ability to mimic the natural function of cortisol produced by the adrenal glands. Data from the European Adrenal Insufficiency Registry (EU-AIR) shows that the majority of patients in Europe, or around 87%, rely on hydrocortisone as the main therapy to treat adrenal insufficiency, whether caused by direct disorders of the adrenal glands (primary adrenal insufficiency) or due to disorders in the hypothalamus or pituitary that regulate adrenal hormone production (secondary adrenal insufficiency) (Murray *et al.*, 2017). In the treatment of adrenal insufficiency, it is important to adjust the dose of hydrocortisone to match the body's needs. If the dose is too low, the body does not get enough cortisol, which can lead to typical symptoms of adrenal insufficiency

such as severe fatigue and metabolic disturbances. In more severe cases, this condition can develop into adrenal crisis, which is a medical emergency characterized by low blood pressure, dehydration, and impaired consciousness. Conversely, if the dosage is too high, the body experiences an excess of cortisol, which can cause symptoms similar to Cushing's syndrome. Therefore, patients with primary adrenal insufficiency require customized replacement therapy to replicate normal daily cortisol levels, so that the body's physiological functions continue to run properly without the risk of hormone deficiency or excess (Hahner *et al.*, 2021).

Adrenal crisis is a medical emergency characterized by serious health problems and accompanied by at least two of the following symptoms: low blood pressure (systolic < 100 mmHg), nausea or vomiting, extreme fatigue, low blood sodium levels (hyponatremia), low blood sugar levels (hypoglycemia), high potassium levels (hyperkalemia), and the condition may improve after parenteral administration of glucocorticoids (by injection or infusion). The main clinical features of adrenal crisis are reduced fluid volume and blood pressure. Symptoms such as nausea, vomiting and diarrhea can worsen the situation by further reducing body fluids, increasing the risk of shock. Glucocorticoids support the effects of catecholamines especially when the cardiovascular system is activated due to stress, by ensuring that blood vessels can contract properly and the heart can work optimally. However, in adrenal insufficiency, glucocorticoid production is impaired, resulting in an ineffective response to catecholamines. In addition, hypovolemia that occurs due to sodium and fluid loss due to aldosterone deficiency also causes blood pressure to decrease further. The combination of hypovolemia and hypocortisolism makes people with adrenal insufficiency more prone to hypotension which can lead to adrenal crisis if not treated immediately (Lousada, Mendonca and Bachega, 2021). If adrenal crisis is suspected, treatment should be started immediately without waiting for test results. Basal ACTH and cortisol sampling before hydrocortisone administration is essential for diagnosis. Continuous hydrocortisone infusion is preferred over injections as it keeps cortisol levels more stable (Prete *et al.*, 2020).

To resolve adrenal crisis, intravenous hydrocortisone 100 mg is given rapidly to maximize the mineralocorticoid effect. Fluid saline administration and treatment of the cause are also important. Fluid saline infusion and continuous intravenous hydrocortisone (200 mg per day) are continued until the patient is stabilized within 24-48 hours (Husebye *et al.*, 2021). Once the initial treatment is successful and the patient's condition improves, the hydrocortisone dose should be lowered slowly, with adjustments based on the patient's response and close monitoring of blood pressure and symptoms. As hypoglycemia is common, intravenous glucose administration may be required. If there is no ongoing inflammation, the patient can be switched to oral hydrocortisone within 24 hours. Intravenous fluids, usually isotonic saline, should be given with close monitoring to avoid worsening or too rapid correction of hyponatremia (Bornstein *et al.*, 2016b; Hahner *et al.*, 2021; Punty, Ramaya; Krsitin, Rachel; Bornstein, 2022).

During high-dose hydrocortisone infusion, mineralocorticoids are not needed. However, when the hydrocortisone dose is reduced to below 50 mg per day, mineralocorticoid therapy may be restarted. Patients may require intensive care, depending on their medical condition (Betterle, Presotto and Furmaniak, 2019).

If hydrocortisone is not available, prednisolone can be used instead at a dose of 25 mg bolus, followed by two doses of 25 mg, totaling 75 mg in the first 24 hours, then 50 mg every 24 hours. Dexamethasone should be avoided and only used (4 mg every 24 hours) if no other glucocorticoids are available (Lousada, Mendonca and Bachega, 2021).

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