

# Diagnosis and Management of Adrenal Crisis in 46XX Congenital Adrenal

*by Nur Rochmah*

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## Case Report

### DIAGNOSIS AND MANAGEMENT OF ADRENAL CRISIS IN 46XX CONGENITAL ADRENAL HYPERPLASIA INFANT

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#### ABSTRACT

Adrenal crisis is the acute complication of the patient with congenital adrenal hyperplasia. Congenital adrenal hyperplasia (CAH) is a rare condition. Children with CAH commonly come to the emergency room due to acute complications. This condition has high mortality and thus needs early recognition. Newborn screening for CAH in Indonesia is not routinely performed and has not been suggested yet. The purpose of this case report was to report a case of adrenal crisis in a congenital adrenal hyperplasia patient focused on diagnosis and therapy. A female, 10 months old infant, was admitted to the emergency department with a chief complaint of a decrease of consciousness for 3 hours before admission and frequent vomiting since born. On physical examination, there was clitoromegaly. Laboratory showed 17-OH progesterone: 173 ng/dL (7-77 ng/dL) and karyotyping: 46XX. Management of adrenal crisis is a stress dose of hydrocortisone and rehydration. Education is the key to optimal outcomes and normal growth and development.

**Keywords:** 46XX; adrenal crisis; congenital adrenal hyperplasia; management; food nutrition improvement; mortality

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## INTRODUCTION

Adrenal crisis (AC) is a life-threatening emergency condition that can occur in patients with adrenal insufficiency. Adrenal insufficiency (AI) is a rare disease associated with a risk of morbidity and mortality. Congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency (called classic CAH) is the most common cause of adrenal steroid insufficiency in pediatric patients (Rushworth & Torpy 2014, Ashrafuzzaman & Rahim 2015).

Congenital adrenal hyperplasia is an autosomal-recessive condition that is caused by deletions or mutations in the CYP21A2 gene. In infants born with ambiguous genitalia, CAH should be suspected. The hormonal gold standard test is to measure the levels of 17-OHP. The CAH is made up of salt wasting and a simple virilized form. In the salt wasting type, people have a history of frequent vomiting since they were born. There is no history of fever. Infections were reported most frequently.

The adrenal crisis incidence remains high, particularly for people with primary adrenal insufficiency, despite the behavioral intervention's introduction (Shepherd et

al. 2022). The adrenal insufficiency new presentation symptoms can range from nonspecific minor symptoms to a life-threatening adrenal crisis with hemodynamic instability (Ten et al. 2001, Charmandari et al. 2014). Signs and symptoms of the adrenal crisis include nausea and vomiting (47%); abdominal, chest, flank, or back pain (86%); confusion (42%); fever (66%); joint aches and muscle; abdominal rigidity (22%); and hypotension or hypovolemic shock (>90%) (Charmandari et al. 2014).

The mortality rate for people with the most severe presentation of adrenal crisis is between 6 and 15 percent, depending on the population studied (Hahner et al. 2015). The world saw many significant changes. Many new technologies were developed, and new ways of living were adopted. There were also many terrorist attacks and natural disasters, which caused a lot of damage and loss of life. The diagnosis of an adrenal crisis is often delayed, with approximately 60% of cases requiring two or more clinician evaluations before diagnosis (Betterle et al. 2019). The adrenal crisis affects approximately 1 in 12 patients with primary adrenal insufficiency each year (Hahner et al. 2015). Patients who have had an adrenal crisis are more likely to experience subsequent episodes, and

every 1 in 200 incidents of AC can be fatal (Allolio 2015).

The prevalence of AC was 5–10 /100 patients/year. The mortality rate is 0.5/100 patients/year (Reisch et al. 2012). The incidence is 1 in 15,000 live births children (Webb & Krone 2015). A large international registry study (34 centers, n= 518 patients, 2,300 patient-years) reported 2.7 adrenal crises per 100 patient-years in children with CAH, with the majority of illness episodes managed at home (Ali et al. 2021).

Through acute stress or illness, the adrenal cortex produces more of the steroid hormone cortisol. Patients with adrenal insufficiency are impotent to naturally produce enough cortisol, the axial response increases glucocorticoids (i.e., cortisol) and mineralocorticoids (i.e., aldosterone), unable to produce a normal physiologic response, hydration during these stressful times to avoid acute adrenal crisis, thus requiring daily steroid replacement therapy during acute stressful times or advised to double or triple their dosage, for example, succeeding a car accident, during an illness, or preceding a surgical intervention (Ten et al. 2001, Grossman et al. 2013, Bancos et al. 2015, Lentz et al. 2022). Failure to take and/or adjust their medication can lead to an adrenal crisis, which can be fatal (Hahner et al. 2015).

Children with classic CAH who had predicted adult height two standard deviations below their MPH treated with GH alone or in combination with a GnRH analog achieved taller adult height compared with their predicted height at baseline (Mallappa & Merke 2022). Overall, there is limited evidence to support the benefits of GH therapy in adults, with or without a GnRH analog. Non-randomized studies, suggest the limitation of recommendation of such growth-promoting therapies in regular clinical practice. This means that it is not currently recommended as a regular treatment option (Speiser et al. 2018).

Severe 21-hydroxylase deficiency in children with CAH results in salt loss, cortisol deficiency, and androgen excess. Infants with renal salt loss tend to have a poor diet, weight loss, growth retardation, vomiting, dehydration, hypotension, hyponatremia, and hyperkalemia. Metabolic acidosis leads to adrenal crisis (azotemia, vascular collapse, shock, and death). A rapid bolus of hydrocortisone can be given intravenously or intramuscularly during an adrenal crisis. To rehydrate, isotonic saline containing D5 is given based on the dehydration degree. Conditions associated with hypoglycemia may require a bolus of dextrose, and if hyperkalemia occurs, ECG abnormalities should be monitored (Hubby et al. 2016). If misdiagnosed, the disease can be fatal, causing coma

and unexplained infant death (Nisticò et al. 2022). It can be challenging to diagnose and manage a case.

## CASE REPORT

A female, 10 months old infant was consulted to the emergency department with a chief complaint of decrease of consciousness for 3 hours before admission. The parents also reported weakness, frequent vomiting, and poor feeding. Vomiting was observed 8 times per day starting from 3 days before. There was a history of fever for 4 days. The patient refused to eat and drink and her last urination was 6 hours before admission.

From the previous history, the patient was regularly controlled at the pediatric endocrinology outpatient clinic (OPC) and received oral hydrocortisone and a salt tablet. Laboratories result confirmed elevation of 17-OH progesterone (173 ng/dL, normal: 7-77 ng/dL), and karyotyping was 46XX.

Physical examination revealed that the infant had unmeasurable blood pressure, heart rate was 246 beats per minute, no palpable pulse, clammy extremity, and capillary refill time > 3 seconds. The respiration was 45x/minute, temperature 38.0°C, and saturation 68% with an O<sub>2</sub> mask of 4 liters per minute. Pediatric GCS was 111, pupils were both 3 mm in diameter, reactive to light, normal physiology, and pathologic reflex examination. There were sunken eyes and intercostal retraction. Rhonchi were noted on both lungs. Skin turgor was decreased. In the genitals, however, there was an enlargement of the clitoris around 10 mm, normal urethral meatus appropriate to Prader 1 (Figure 1 (A) and (B)). Her body weight was 5 kg, height was 56 cm. No rash and cyanosis were found.

Electrocardiography showed ventricular fibrillation. Random blood glucose was <20 mg/dL. The patient got cardiopulmonary resuscitation, intravenous dextrose 10% 10 ml, and NaCl 0.9% 100 ml after 60 seconds, the ECG rhythm back to sinus, blood pressure was 85/45 mmHg, pulse rate was 190 beats per minute, palpable pulse; respiration rate 35 times per minute, temperature 38.2°C and saturation was 99% with O<sub>2</sub> mask Jackson Reese 8 liter per minute and planned for intubation. The patient was also given a hydrocortisone iv 50 mg bolus, followed by hydrocortisone 3x15 mg iv, and continued with oral 15 mg hydrocortisone and 0.1 mg fludrocortisone.

The laboratory examination revealed leukocyte was 17.590/mm<sup>3</sup>, hemoglobin 8.7 g/dl, hematocrit 22.9%, platelet 217.000/mm<sup>3</sup>, sodium 137 mmol/L, potassium 8.05 mmol/L, chloride 99 mmol/L, calcium 10 mmol/L, Blood Urea Nitrogen 74 mg/dL, creatinine

Serum 4.43 mg/dL, Albumin 4.37 g/dL, AST 61 U/L, ALT 144 U/L, Blood Gas pH 7.29, pCO<sub>2</sub> 14, pO<sub>2</sub> 137.3, HCO<sub>3</sub> 6.9, BE -19.7, and SO<sub>2</sub> 99. Urinalysis glucose negative, ketone negative, pH 5.0, protein negative, nitrate negative, erythrocyte 0-1, and leucocyte 0-2. The patient was planned for intravenous insulin, dextrose, and sodium bicarbonate for potassium correction and calcium gluconate for calcium correction. The chest x-ray examination showed within the normal limit (Figure 2). 213037

The patient was born with mature gestation of 38 weeks, birth weight was 3,700 grams, length of 48 cm, and delivered normally. She cried immediately after birth, there was no history of cyanosis and jaundice. Immunization history was up to date (BCG, hepatitis B, DPT, polio, measles) in primary health care. Growth and development history revealed that the patient lifted her head on 5 months of age, sitting with support on 10 months of age, could not stand on her own, and could not say any phrase. The patient was breastfed from birth until 6 months, receiving formula milk since the age of 5 months, and rice porridge since the age of 6 months. She is the fourth child of four siblings of Javanese ethnicity. There were no relatives with a history of an endocrine disorder, a disorder of sex development and malignancy.



Figure 1. Picture of the 10-months-old patient with adrenal crisis (A) and congenital adrenal hyperplasia characterized by clitoromegaly (B)

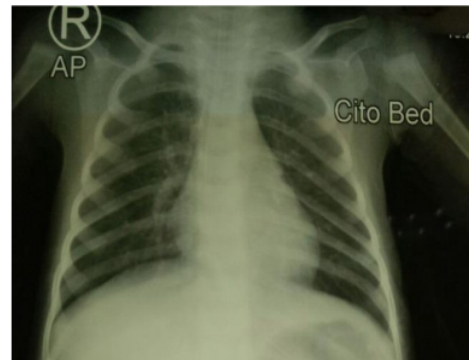


Figure 2. Normal chest x-ray

The patient was also planned for blood glucose and serum electrolyte monitoring and then was transported to PICU. She remained stable over the first night of admission. She was successfully weaned off from ventilator support on the third day of hospitalization. After the condition improved and extubated, the patient was switched to oral hydrocortisone 3 mg every 8 hours (15 mg/m<sup>2</sup>/day), fludrocortisone 0.1 mg every 24 hours orally, and a salt tablet. She was ultimately discharged on day 7 of admission in good condition. Currently, the patient was in stable condition and routinely controlled for pediatric endocrine OPC.

On follow-up, the patient was in stable condition and routine control in OPC and had taken the medication. The patient was planned to perform clitororeduction.

## DISCUSSION

The patient came with an acute emergency with decreased consciousness, shortness of breath, and clammy extremities with a history of frequent vomiting without any fever. The patient was previously diagnosed with CAH and received medicines. Adrenal crisis is acute deterioration in a patient with adrenal insufficiency. The principal clinical manifestation is hypovolemic shock, coma, and marked laboratory which necessitates immediate treatment (Bouillon 2006).

Inadequate cortisol production can lead to hypoglycemia followed by hypotension and fatigue. The symptoms of the illness are more likely to be observed in younger children during periods of sickness or stress. Children with congenital adrenal hyperplasia have low cortisol responses to hypoglycemia (Bowden & Henry 2018). There are 2 types of CAH, the classic and nonclassical. The first type, the classic form, is commonly caused by 21-hydroxylase deficiency. It is a genetic disorder that results in impaired biosynthesis of cortisol with and without aldosterone and epinephrine deficiency. CAH is an autosomal recessive inherited. The clinical manifestation is varied, starting from most severe to mild forms, depending on the degree of severity of the gene defect (Krone & Arlt 2009). Adrenal crisis can be the first clinical presentation of patients with CAH.

Patients with adrenal insufficiency are often in hypotensive shock and may have paresthesias. They frequently have gastrointestinal symptoms like abdominal pain, nausea, vomiting, diarrhea, and leading to an erroneous diagnosis of an acute abdomen or gastroenteritis. Hypotension is secondary to hypovolemia, but is also due to hypocortisolism, as glucocorticoids exert a permissive effect on catecholamine action (Arlt & Allolio 2003, Verbalis et al. 2013, Puar et al. 2016). Electrolyte imbalance and hyponatremia are due to aldosterone deficiency. It leads to natriuresis, decreased fluid volume, and hyperkalemia. CAH hypercalcemia can be caused by decreased renal excretion of calcium and increased bone resorption (Arlt & Allolio 2003).

About 80% of AC is precipitated by concomitant events. The most important trigger factors are respiratory and gastrointestinal infections (Ishii et al. 2018). The majority of patients suffered from AC between 1 and 3 years old, when the respiratory or

gastrointestinal infection is usually relatively prevalent (Reisch et al. 2012).

Table 1. Precipitating factor for an adrenal crisis in children with 21-hydroxylase deficiency (21-OHD)

Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%
Gastroenteritis	33.3%
Upper respiratory infection	30.2%
Lower respiratory infection	10.4%
Flu	4.2%
Urinary tract infection	2.1%
Others	6.3%
No known factor	12.5%

Source: Ishii et al. (2018)

Ventricular fibrillation can be induced by hypoglycemia and hyperkalemia. Hypoglycemia is associated with significant lengthening of the corrected QT interval ( $QT_c$ ) (Laitinen et al. 2008). It is due to increased catecholamine release during hypoglycemia. The  $QT_c$  prolongation could lead to a high risk of ventricular fibrillation and sudden death (Robinson et al. 2003). As potassium increases, the resting membrane potential continues to become less negative, and progressively decreases  $V_{max}$ . The early effect of mild hyperkalemia on myocyte function is to increase the excitability by shifting the resting membrane potential to a less negative value and thus closer to threshold potential; but as potassium levels continue to rise, myocyte depression occurs and  $V_{max}$  continues to decrease (Parham et al. 2006).

Hypotension in AC can be explained by a lack of the permissive action of glucocorticoids on adrenergic receptors (Sapolsky et al. 2000), and by volume depletion caused by a lack of sodium and fluid retention due to missing mineralocorticoid activity. Volume depletion may further be worsened by vomiting and diarrhea (Bancos et al. 2015).

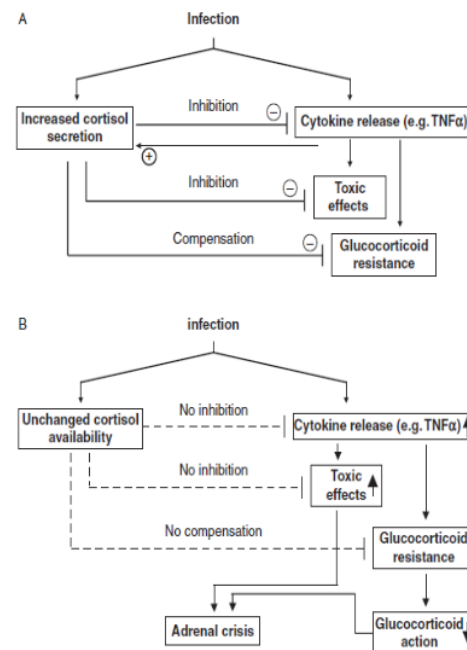
For adrenal crisis patients with hypotension, the resuscitation strategy is similar to treating patients with sepsis (Lentz et al. 2022). The basic management components of include treating an underlying etiology, stress dose steroids, i.e., fluid resuscitation, glucose, and electrolyte correction. The patient either as a

primary presentation of adrenal insufficiency or a known history of adrenal insufficiency with an acute stressor often presents in undifferentiated shock (Charmandari et al. 2014). Empirical management of adrenal insufficiency should be considered in patients with limited history and undifferentiated shock. Fever can occur as a symptom of glucocorticoid deficiency or infection. If sepsis is suspected, routine treatment should include cultures followed by empirical antibiotics. Rapid rehydration with 1000 mL of 0.9% saline is recommended (Charmandari et al. 2014, Allolio 2015). The additional fluid administration and fluid composition can then be adjusted based on clinical assessment and electrolyte abnormalities. If hypoglycemia is present giving dextrose-containing fluids are recommended (Charmandari et al. 2014).

Fever and infection lead to an increase in circulating cortisol levels in healthy subjects. Increment in cortisol levels should be mimicked by adjustment of the hydrocortisone dose in patients with adrenal insufficiency (Husebye 2014). Glucocorticoids influence stress response by permissive, suppressive, stimulatory, and preparative actions (Sapolsky et al. 2000), while a lack of permissive action of glucocorticoids is highly likely in patients with undiagnosed adrenal insufficiency leading to impaired activation and responsiveness of the cardiovascular system (Sapolsky et al. 2000).

Infections include interleukin 1 (IL-1), which physiologically stimulates the hypothalamic-pituitary-adrenal (HPA) axis, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin 6 (IL-6), induced the release of cytokines. As a result, cortisol levels increase (Silverman et al. 2005). High levels of glucocorticoids reduce the release and action of cytokines and prevent their potentially harmful effects (Koniaris et al. 2001). Studies have shown that TNF- $\alpha$  inhibits the function of glucocorticoid receptors and induces a relative state of glucocorticoid resistance (Webster 2001, Bogaert et al. 2011). Lack of glucocorticoid inhibitory activity can induce AC through increased TNF- $\alpha$  secretion, increased TNF- $\alpha$  sensitivity, and TNF- $\alpha$ -induced glucocorticoid resistance.

Acute treatment of adrenal crisis is for stabilization and rehydration, and rapid restoration of tissue perfusion. After an IV line is secured, a 20 mL/kg bolus of normal saline (0.9% NaCl) is given over for a period of an hour.



Source: Allolio B (2015)

Figure 3. Glucocorticoid and cytokine interaction during major infection in patients with intact adrenals (A) and patients with adrenal insufficiency on standard replacement therapy failing to adjust their hydrocortisone doses (B).

If significant hypoglycemia is present, the glucose of bolus 0.2 g/kg (2 mL/kg of 10% dextrose) is given to revive the blood glucose level. Stress doses of glucocorticoid should be administered with a loading dose. Hydrocortisone contains a desirable mineralocorticoid effect in addition to its glucocorticoid effect, whereas methylprednisolone and dexamethasone have only a glucocorticoid effect and do not seem to be suitable therapies (Miller et al. 2008, Ucar et al. 2016).

Ongoing IV steroid therapy consists of hydrocortisone (HC) with a total daily dose of 15-20 in 3 divided doses every 6-8 hours. Hyperkalemia of more than 6 mmol/L can induce fatal cardiac arrhythmias and requires aggressive therapy with intravenous sodium bicarbonate, calcium gluconate, or IV dextrose plus insulin (Parham et al. 2006, Miller et al. 2008).

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Table 2. The anti-inflammatory comparison, mineralocorticoid, growth suppressing, and androgen suppressing side effects of commonly used steroids.

Steroid	Anti-inflammatory effect	9 Growth suppressing, glucocorticoid effect, androgen suppressing effect	Salt retention, mineralocorticoid activity
Hydrocortisone	1	1	1
Prednisone	4	5-15	0.8
Prednisolone	3.5-4		0.8
Methylprednisolone	5		0.5
Betamethasone	30	0-100	0
Dexamethasone	30	0-100	0
Fludrocortisone	15		200

Source: Ucar et al. (2016)

1  
Education is very important in the management of adrenal insufficiency and the prevention of AC. Patients and families should be informed about CAH, general CAH management, and acute complications which should be taken at home to prevent an adrenal crisis, particularly related to glucocorticoids adjustments in stressful events and AC prevention including administration of emergency glucocorticoid particularly in illness, fever, and any type of stress (Lousada et al. 2021). Furthermore, the general practitioners, pediatricians, nurses, and health workers must be aware of these cases. The early detection and prompt treatment can improve the prognosis and quality of life of patients with CAH and AC. Recently, the CAH screening has already been included in the newborn screening suggested in Indonesia.

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Prognosis in patients with AC and the mortality of patients with peripheral adrenal insufficiency are increased in some studies. The quality of life of patients with peripheral adrenal insufficiency remains impaired despite the adequate replacement dose but seems to be related to the delay in diagnosis (Nowotny et al. 2021).

Congenital adrenal hyperplasia is a rare condition. In Indonesia, newborn screening for CAH is not routinely performed and has not been suggested yet. Children with CAH commonly come to the emergency room due to acute complications such as adrenal crisis. This condition has high mortality and thus needs early recognition. The diagnostic test for CAH (chromosomal and enzyme) can be performed only in a particular laboratory. The management limitation in this case is fludrocortisone is not yet available in Indonesia, thus becoming a challenge in the management of patients with CAH.

## CONCLUSION

The diagnosis of adrenal crisis should be performed as soon as possible to lower the mortality rate and improve the prognosis and quality of life of the patient. Moreover, in patients with shock, and history of disorder of development, especially CAH, the clinician must include an adrenal crisis in the differential diagnosis.

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