

Salt-Wasting Congenital Adrenal Hyperplasia in A 2-Year-Old Patient

Nanda Amelia¹, Tenri Esa^{1,2}, Liong Boy Kurniawan^{1,3}, Ratna Dewi Artati⁴

¹Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University/Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia. E-mail: nandooamelia@gmail.com

²Dadi Regional Hospital Laboratory Installation, Makassar, Indonesia

³Clinical Pathology Laboratory, Hasanuddin University, Makassar, Indonesia

⁴Department of Pediatrics, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

ABSTRACT

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder due to deficiencies of enzymes involved in steroidogenesis in the adrenal cortex. It is known that 90% of CAH are due to 21-hydroxylase enzyme deficiency caused by mutation of the CYP21A2 gene. A female patient aged two years and one month old was reported with a diagnosis of salt-wasting CAH. The diagnosis was based on complaints of genital enlargement since birth. The patient had developed repeated vomiting and severe dehydration since newborn. The patient was diagnosed with CAH and under treatment with glucocorticoid replacement therapy by a pediatrician since the age of 5 months. Body height/age <-3 Standard Deviation (SD) of the Z-score chart (very short stature) and ambiguous genitalia were reported. Laboratory tests indicated thrombocytosis (795x103/ μ L), mild hyperkalemia (5.4 mmol/L), and increased testosterone (110.1 ng/dL). Bone age study affirmed an advanced bone age. History of increased 17-hydroxyprogesterone (109.19 ng/mL) and decreased morning serum cortisol levels (1.7 μ g/dL). History of gynecological ultrasonography (USG) showed uterus, no bilateral testicular structure, hyperplasia of the left adrenal gland, and suggestive of genital ambiguity. The 21-hydroxylase deficiency causes a decrease in aldosterone and cortisol and an increase in androgens. Hypoaldosteronism causes hypovolemia, hyponatremia and hyperkalemia. Hypocortisolism causes hypoglycemia, decreased response to infection, and stress. Hyperandrogenism causes virilization of the genitalia and short stature in patients. A female patient aged two years and one month old was reported with a salt-wasting congenital adrenal hyperplasia diagnosis. Chromosome analysis was the recommended test in this case.

Keyword: Congenital adrenal hyperplasia, salt-wasting, a girl

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders caused by an enzyme deficiency needed for steroidogenesis in the adrenal cortex.¹⁻⁴ Steroid synthesis (Figure 1) takes place in three zones of the adrenal cortex in 3 zones, namely the zona glomerulosa, which secretes mineralocorticoids (aldosterone). The zona fasciculata secretes glucocorticoids (cortisol), and the zona reticularis, which secretes androgens.⁴ A deficiency of the 21-hydroxylase enzyme causes more than 90% of CAH due to a partial deletion in the CYP21A gene on chromosome 6 (6p21.3).¹⁻⁵

Congenital adrenal hyperplasia due to deficiency of the 21-hydroxylase enzyme can be classified into classic CAH, which consists of Salt-Wasting (SW), Simple Virilizing (SV), and non-classical or late onset CAH.^{1,2,4} Incidence of classic CAH is one among 12,000 to 15,000 live births worldwide. A study in England found that each child of 18,000 births has CAH. Data from Cipto Mangunkusumo Hospital from

1985 to 2005 reported 25 cases of CAH, whereas data from Dr. Soetomo Hospital, Surabaya, from 1997 to 2011 reported 19 cases of CAH. There were 32 CAH patients reported by the Laboratory Center for Biomedical Research, Faculty of Medicine, Diponegoro University, Semarang from 1991 to

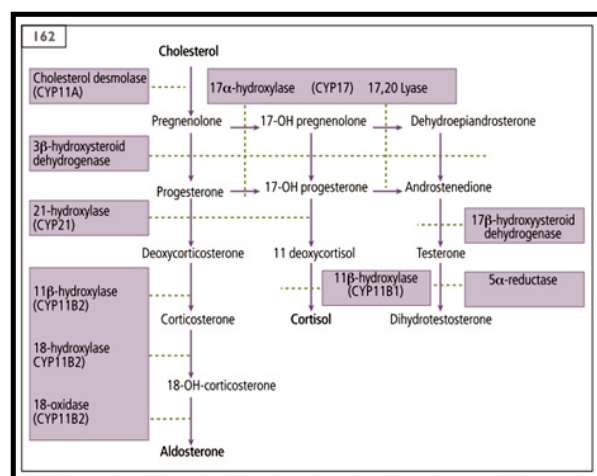


Figure 1. Steroid biosynthesis in adrenal cortex⁴

2008.^{2,6,7} Data of Dr. Wahidin Sudirohusodo Hospital until 2021 recorded 7 CAH patients and 3 of them had salt-wasting CAH.

CASE

A 2-year-old girl came to the pediatric endocrine Outpatient Clinic at Dr. Wahidin Sudirohusodo Hospital (RSWS) for treatment control. The patient's mother complained of continuous vaginal enlargement that she had experienced since birth. Patients were frequently admitted to the hospital with symptoms of repeated vomiting and diarrhea accompanied by severe dehydration from 1 month until the current referral to (RSWS). The patient was diagnosed with congenital adrenal hyperplasia and routinely underwent glucocorticoid treatment from a pediatrician at the hospital since she was five months old.

The patient was first admitted to RSWS at the age of 5 months and four days with complaints of vomiting (6 times a day), diarrhea, and general condition of weakness, sunken eyes, feeling thirsty, good turgor and ambiguity in the genitalia (phallus 1.6 cm). The patient was investigated for the cause of genital ambiguity by measurement of 17-OH-progesterone levels, testosterone levels, morning serum cortisol, and blood electrolyte levels with a result of 109.19 ng/ml (N: <1.70 ng/mL), 11.18 ng/dL, 1.7 µg /dL (N: 3.7-19.4 µg/dL), hyponatremia (111 mmol/L), hyperkalemia (6.0 mmol/L), and hypochloremia (85 mmol/L), respectively. The results of the gynecological ultrasound showed a uterus but absent bilateral testicular structures, left adrenal gland hyperplasia, and suggestive of genital ambiguity. After 11 days of treatment, the patient recovered and was allowed to be outpatient with hydrocortisone therapy of 2.5 mg/day and salt supplementation of 1-2 grams/day given since the patient was five months old.

The patient is the last child of three siblings. The patient's second brother died at the age of 4 months due to congenital heart disease. The eldest brother is nine years old and grows up in good health. No similar complaints were found in either parents or other family members.

The mother was pregnant with the patient at the age of 31 years; mother routinely underwent pregnancy control at the health center and received vitamins and blood-boosting substances. There was no history of fever and vaginal discharge. The patient was delivered by cesarean section with an immediate cry, unknown APGAR score, birth weight of 2,800 grams, birth length of 48 cm, and sufficient gestational age. The patient was breastfed from birth to 6 months old. The patient had completed the basic immunization requirement.

PHYSICAL EXAMINATION

Body Weight (BW): 8 Kg, Body Height (BH): 73 cm, BW/BH: between -1 and -2SD (good nutrition), BH/age: Located below the -3SD line of the Z-score curve (very short stature), BW/age: Located below the -3SD line (very underweight). Interpretation: Good nutritional status and very short stature.



Figure 2. The physical appearance of a patient
(Source: personal documentation)

General condition: Mild illness/composmentis/ GCS 15/normal nutritional status; Vital signs: Blood pressure: 100/70 mmHg; Pulse: 110 times/minute. Respiration: 28 times/minute; Temperature: 36.9°C. Oxygen saturation: 100%; Head: Head circumference: 43 cm (normal: 45.7-48.6 cm). Interpretation: microcephaly. Neck: No lymph node enlargement; Thorax: vesicular breath sounds, no rhonki and wheezing. Normal first and second heart sounds. No heart murmur was found; Abdomen: normal peristalsis, liver, and spleen were not palpable; Extremities: warm extremities, no edema, CRT < 2 seconds; Genitalia: vagina (+), vulva (+), phallus length of 2.2 cm (Prader 1), there were a vaginal opening and urinary tract. There was no scrotum and penis (Figure 3).

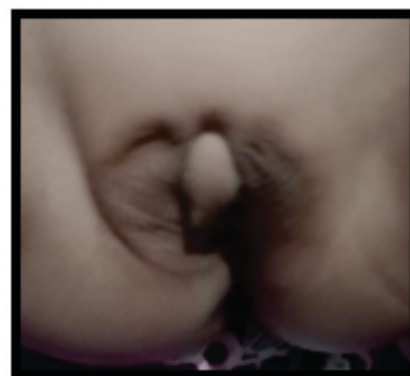


Figure 3. Genital of patient
(Source: personal documentation)

LABORATORY TEST RESULTS

Table 1. Blood routine test results on 03/03/2021

Parameter	Results	Reference Value
Hemoglobin	12.8	9.6 – 15.6 (g/dL)
Hematocrit	38	34.0 – 48.0 (%)
Erythrocyte	5.35	4.00 – 5.20 ($10^6/\mu\text{L}$)
MCV	71	76.0 – 92.0 (fL)
MCH	24	23.0 – 31.0 (pg)
MCHC	34	32.0 – 36.0 (g/dL)
RDW-CV	13.9	11.5 – 14.5 (%)
Leukocyte	13.3	5.50 – 17.50 ($10^3/\mu\text{L}$)
Platelet	795	150 – 450 ($10^3/\mu\text{L}$)
Neutrophil	28.5	22-46 (%)
Lymphocyte	58.6	37-73 (%)
Monocyte	7.5	2-11 (%)
Eosinophil	4.7	1-4 (%)
Basophil	0.7	0.0-2.0 (%)

Interpretation: Thrombocytosis

Table 2. Results of blood chemistry and electrolyte tests on 03/03/2021

Parameter	Results	Reference Value
Random blood glucose	84	140 (mg/dL)
Sodium	134	136-145 (mmol/L)
Potassium	5.4	3.5-5.1 (mmol/L)
Chloride	103	97-111 (mmol/dL)

Interpretation: Mild hiperkalemia

Table 3. Results of follow-up endocrinology tests on 15/03/2021

Parameter	Results	Reference Value
Testosterone	110.1 (ng/dL)	Female, 8-18 years Tanner stage: 1: <2.5-6.12; 2: <2.5-10.4; 3: <2.5-23.7; 4: <2.5-26.8; 5: 4.6-38.3

Interpretation: Elevated testosterone levels

SUPPLEMENTARY TEST RESULTS

Bone age assessment (08/03/2021): Bone age was estimated to range between 2 years and eight months to 3 years and six months (Greulich and Pyle method) (Figure 4).

CLINICAL DIAGNOSIS

Classic congenital adrenal hyperplasia with salt-wasting type.



Figure 4. Bone age assessment of sinistra (Source: personal documentation)

DISCUSSIONS

Based on medical history, physical examination, and laboratory test results, the patient showed symptoms of CAH with salt-wasting type. The patient received hydrocortisone oral therapy of 6 mg/24 hours and table salt supplementation of 1-2 grams/day.

Routine blood test results in this study indicated a condition of thrombocytosis ($795 \times 10^3/\mu\text{L}$). It was presumed that the patient had reactive thrombocytosis. Stress, infection, and inflammation, which stimulate proinflammatory cytokines, are several factors that may induce reactive thrombocytosis characterized by excessive platelet production. Patients with CAH have low cortisol levels, which leads to a weakened response to infection and stress. It was then suspected to be the cause of thrombocytosis in patients. However, suspicion of essential thrombocytosis was not ruled out because peripheral blood analysis or bone marrow puncture was not carried out.^{2,3}

Deficiency of 21-hydroxylase prevents the conversion of progesterone to deoxycorticosterone (aldosterone precursor), thereby causing aldosterone deficiency.^{2-4,8} Aldosterone deficiency disrupts sodium homeostasis, leading to excessive sodium excretion through the urine, thereby causing hyponatremia in patients. Natriuresis will be followed by osmotic diuresis, which can lead to hypovolemia and shock. Currently, no hyponatremia (134 mmol/L) due to routine glucocorticoid therapy and daily salt supplementation was found in the patient. However, the patient had a history of recurrent hyponatremia. Low aldosterone also interferes with the excretion of potassium, which leads to a high risk of hyperkalemia as found in the patients with potassium levels of 5.4 mmol/L categorized as mild hyperkalemia.^{1-3,8}

Deficiency of 21-hydroxylase also disrupts the conversion of 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor).¹⁻⁴ Therefore, there is an accumulation of 17-hydroxyprogesterone in patients with a history of 17-OH progesterone (109.19 ng/mL). Impaired cortisol formation will lead to increased secretion of Adrenocorticotrophic Hormone (ACTH) by the pituitary gland, which will eventually result in enlargement of the adrenal glands, accumulation of steroid precursors, and excessive production of adrenal androgens.^{3,4}

Inadequate cortisol levels also decrease the gluconeogenic process and lead to hypoglycemia. Although the patient did not experience hypoglycemia (GDS: 84 mg/dL), the patient experienced a history of hypoglycemia on the last treatment with the lowest blood glucose level of 27 mg/dL (April 2020).^{7,9} Low cortisol can cause weakness and low tolerance to stress and infection. Elevated androgens cause varying degrees of virilization of the female external genitalia. It explains the grade 1 praderma in the genitalia of patients with a 2.2 cm phallus. Hyperandrogenism causes highly rapid bone growth until puberty, and there will be faster closure of the bone epiphyses, resulting in very short stature (BH/age: located below the -3SD line). This process was supported by the radiology results of the patient's left manus bone age, with an estimated bone age of 2 years eight months to 3 years six months, indicating that it was older than the patient's actual age. This finding could explain the pathomechanism of the history of low morning serum cortisol levels and elevated testosterone control of 1.7 µg/dL and 110.1 ng/dL, respectively.^{1-4,7,10}

According to the Prader scale, the patient in this study suffered from stage I virilization and was treated for five months; therefore, no surgical correction was performed. The latest surgical approach for female CAH patients with virilization 3-4 based on the Prader scale is to perform a single-stage surgical procedure at the age of 2-6 months, namely by performing clitoroplasty and vaginoplasty simultaneously. Adrenalectomy is performed in some cases. However, this procedure is limited to females with hyperandrogenic symptoms, which do not improve along with optimal corticosteroid replacement therapy.^{2,4,10}

The differential diagnosis, in this case, was diseases that cause genital virilization, such as androgen-secreting tumors, placental aromatase deficiency, true hermaphrodite, maternal androgens through the placenta (consumption of progesterone or danazol, maternal androgen-secreting tumors). In addition, the differential diagnosis for late-onset CAH cases is Polycystic Ovarian Syndrome (PCOS).⁴

Recommended laboratory tests for patients include the ACTH stimulating test, Plasma Renin Activity (PRA), chromosomal analysis (assessing the patient's gender and genetic tests (assessing gene mutations)).^{1-3,5} Treatment for CAH uses glucocorticoids such as Hydrocortisone, Cortisone Acetate, Prednisone, Prednisolone, and Dexamethasone. Hydrocortisone is the therapy of choice because cortisone changes in the liver to activate cortisol and has the least effect on growth suppression. The glucocorticoid given to these patients is hydrocortisone 10-20 mg/m² body surface area per day. The patient was given supplementation of table salt (NaCl) 1-2 g/day (17-34 mmol) per day. These drugs are lifelong treatments and require close monitoring of the clinical condition, electrolytes, dehydration status, and body weight during the adrenal crisis.^{2,4,9}

The prognosis of patients with CAH is ambiguous. Congenital adrenal hyperplasia patients with salt wasting type can die after birth due to adrenal crisis if not treated immediately. Early diagnosis can prevent the adverse effects of CAH, such as improper identification, emergencies due to electrolyte disturbances, adrenal crises, and precocious puberty. Contrastingly, the prognosis *qua ad sanationem* (healing) is *dubia*.^{1,3,4}

CONCLUSIONS

A female patient aged two years and one month old was reported with the diagnosis of salt-wasting CAH. The diagnosis was based on anamnesis, physical examination, and supplementary tests. Chromosome analysis was recommended in this case to determine the correct sexuality of the patient.

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