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A woman with primary amenorrhea due to non-Classical congenital adrenal hyperplasia

Bayu Aji H[1]*, Hermina Novida[2]

[1,2]*Fakultas Kedokteran Universitas Airlangga-RSUD Dr. Soetomo Surabaya, Indonesia*

Abstract

Primary amenorrhea is a condition characterized by the absence of menarche at the age of 14 without secondary sexual development or at the age of 16 with normal secondary sexual characteristics. One of the rare etiologies is Non-Classical Congenital Adrenal Hyperplasia (NCAH), an autosomal recessive disorder caused by 21-hydroxylase deficiency resulting from a mutation in the CYP21A2 gene. This case report presents a 26-year-old woman with primary amenorrhea and ambiguous genitalia who identified herself as male. Clinical examination revealed underdeveloped breasts, the presence of pubic hair, external genitalia resembling a penis with hypospadias-like features, and the absence of menstruation. Laboratory results showed elevated testosterone and 17-hydroxyprogesterone levels, while karyotype analysis confirmed 46, XX. Imaging through ultrasound and MRI demonstrated a rudimentary uterus, vagina, and bilateral adrenal hyperplasia. The patient was diagnosed with non-classical congenital adrenal hyperplasia presenting as primary amenorrhea. Management requires a multidisciplinary approach, including endocrine, urological, and psychological evaluation, with consideration for hormonal therapy and possible reconstructive surgery according to patient preference. This case emphasizes the importance of early diagnosis, comprehensive investigation, and patient-centered decision-making in NCAH with primary amenorrhea to improve quality of life and reproductive outcomes.

Keywords: Primary amenorrhea, Non-Classical congenital adrenal hyperplasia, 21-Hydroxylase deficiency, Case report

Introduction

Menarche at age 14 with no secondary sex growth or no menstruation at age 16 with normal secondary sex growth is known as primary amenorrhea. Amenorrhea is known to occur in about 3 to 4% of the population of reproductive age, and about 10 to 15 percent of patients have primary amenorrhea. Genetic disorders are the most common cause of primary amenorrhea, with 43%, and the smallest causes are hymen imperforate, Androgen Insensitivity Syndrome (AIS), Congenital Adrenal Hyperplasia (HAK), and central nervous system disease, each of which is known to have a frequency of about 1.2%. There are two ways in which adolescent evaluation can be done: through an approach with the patient or through an approach that relies on anamnesis or history, examination, and basic investigation (Hayden and Balen, 2007; Chowdhury *et al.*, 2015).

Congenital Adrenal Hyperplasia (HAK) is one of the endocrine disorders that can cause primary amenorrhea, with a frequency is 1%. There are three phenotypes of HAK: the classic type of HAK, namely *classical salt wasting* and *classical simple virilizing* from birth, and non-classical HAK with late-onset of both symptoms and diagnosis, where prenatal is unknown. Non-classical HAK is caused by a deficiency of the enzyme P450C21 (21-hydroxylase), which is an autosomal recessive disorder caused by a mutation of the CYP21A2 gene. It is reported that the prevalence of non-classical HAK in women with increased androgens ranges from 0.6% to 9% (Trakakis *et al.*, 2008; Witchel, 2013).

Non-classic HAK can appear at various ages with a variety of hyperandrogenic symptoms. In nonclassical HAK, there was a mild deficiency of the enzyme 21-hydroxylase, which was diagnosed based on an increase in serum 17-hydroxyprogesterone (17-OHP). Just like in classic type HAK, non-classical HAK can occur, such as premature growth of pubic hair, rapid bone growth, and rapid linear growth acceleration. In women, symptoms of androgen overload include acne, hirsutism, infertility, menstrual disorders, anovulation, and ambiguous sex (Witchel, 2013). The diagnosis of non-classical HAK must be distinguished from classical HAK, apart from the anamnesis and clinical manifestations, as well as from the results of supporting examinations, namely laboratory examinations and radiological

Correspondence: Bayu Aji H, Fakultas Kedokteran Universitas Airlangga-RSUD Dr. Soetomo Surabaya, Indonesia, **e-mail:** drbahw8411@gmail.com, **Received:** August 29, 2025 **Accepted:** October 30, 2025

examinations. The management given for non-classical HAK is different from the classic HAK. Management given early will give different results. Monitoring also needs to be done for therapeutic evaluation (Speiser *et al.*, 2010; Khattab and Marshall, 2019).

In this case review, we will discuss a 26-year-old woman who suffers from non-classical HAK with primary amenorrhea.

Identity Of the sufferer

The patient named Mr. Hab is 26 years old from Gresik City, Madura tribe, unmarried, and his last education was in high school.

Main complaint:

Abnormal penis

Current disease history

The patient complains of the abnormal shape and size of the penis. The patient complains when the erection curves downwards and feels that when urinating, it does not pass through the ducts that are at the end of the penis. The patient has felt this for approximately 10 years. Pain when an erection is denied. The patient also complained that her breasts were not growing. Currently, the patient plans to get married and wants to be able to have sex normally. The patient has never had a period in his entire life. The patient has never experienced episodes of seizures since childhood, has never experienced hair loss, has no complaints of progressive headaches, no complaints of cough, tightness, chest pain, fever, nausea, vomiting, or weight loss. Bowel movements are felt within normal limits. Skin, range of motion, bones, and muscles are within normal limits. The patient is very anxious about the condition of his penis.

History of past Illness

The patient had no history of Diabetes Mellitus (DM), heart disease, kidney disease, Hypertension (HT), or Tuberculosis (TB) treatment. No other family members have a similar disorder.

Social history: Patients work daily as freelance laborers in the city of Gresik.

Physical examination: (july 1, 2022)

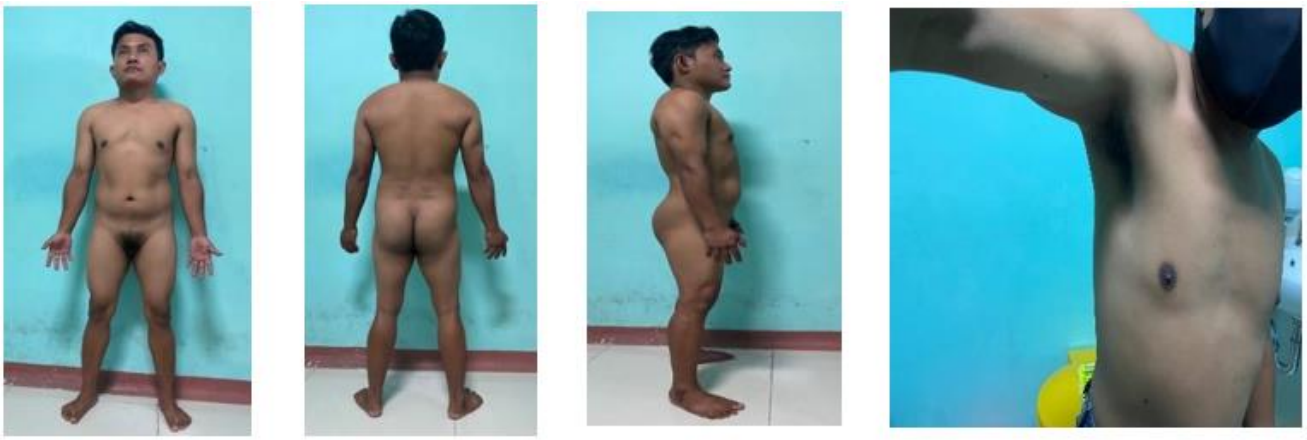
General state of weakness, *composing consciousness (CM), Glasgow Coma Scale (GCS)* 456, *Wong Baker FACEScale 0*, blood pressure (TD) 120/80 mmHg, pulse 84 times per minute, breathing 20 times per minute, axillary temperature 36.8°C, oxygen saturation 98% under space conditions. Weight 55 kg, height 152 cm, body mass index (BMI) 23 kg/m2.

On the examination of the head and neck, it was found that the conjunctiva was not anemic, the sclera was not icteric, there was no cyanosis on the lips, there was no *dysnea*, there was no enlargement of the lymph nodes, and the *jugular venous pressure* did not increase.

Physical examination of the lungs, inspection found symmetrical movement of the right and left chest, and no substernal retraction. Palpation examination found symmetrical palpable phlebosis. Percussion is *obtained* sonorously. Auscultation obtained the sound of vesicular breathing, no *rhonchi* sound or *wheezing,* and no signs of sinusitis.

The heart examination found single S1 and S2 heart sounds, no heart noise or *gallop rhythm*. The results of the abdominal examination at the inspection did not show distension, auscultation of normal intestinal noise, percussion was obtained tympanic, and the liver and spleen were not palpable on abdominal palpation. No leg edema was found.

The genitourinary status was not determined by surgical scars or mass palpation; there was no kidney tap pain, and there was no bulging enlargement. The external genitalia resembled a penis, approximately 6 cm long. It appears that the scrotum is divided into two separate sacs. The external urethral estuary is visible in the lower region at *the penoscrotal transition.* There is no feeling of the testicles, and there is no visible vagina. Spontaneous urine production is approximately 1500 cc in 24 hours. On rectal examination, the tone of the sphincter ani was found to be normal, the mucosa was smooth, but not palpable.



Gambar 1. Gambar Klinis Pasien

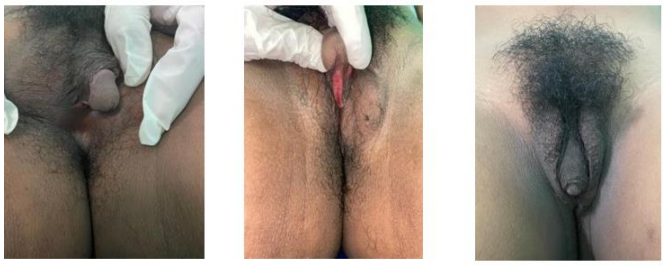


Figure 2. External Genitalia Images of Patients

Supporting examinations

From the results of a laboratory examination at Dr. Soetomo Hospital on July 1, 2022, leukocytes were obtained at 9,740 /µL, hemoglobin 16.2 g/dL, platelets 270,000/µL, *SGOT* 25 U/L; *SGPT* 45 U/L, albumin 4.3 gr/dL, creatinine 0.9 mg/dL, *BUN* 4 mg/dL, random blood sugar 88 mg/dL, sodium 142 mMol/L, potassium 3.5 mMol/L, chloride 106 mMol/L. Urinalysis with a pH of 7.5 and no presence of leukocytes or erythrocytes in the urine, Faal hemostasis is not elongated. Our hormonal parameter checks found estradiol (E2) 54.77 (<87pg/mL), 17-OHP 52.29 ng/ml (0.32-3.07), LH <0.1 mIU/mL with normal values in males (1.1-2.5mIU/mL) and in females (Folicular phase: 1.2-12.5mIU/mL, Ovulatory Phase: 12-82mIU/mL, Luteal Phase: 0.4-19mIU/mL, Postmenopause: 14-48mIU/mL, Males 1.5-11.8mIU/mL), FSH <0.1 mIU/mL with normal values in females (Folicular phase: 3.2-15mIU/mL, Ovulatory Phase: 7.5-20mIU/mL, Luteal Phase: 1.3-11mIU/mL, Postmenopause: 36-138mIU/mL). Testosterone 9.788 ng/mL (Male 2.2-10.5ng/mL). Meanwhile, chromosomal analysis was carried out, and the results were 46.XX were obtained in 20 cells examined.

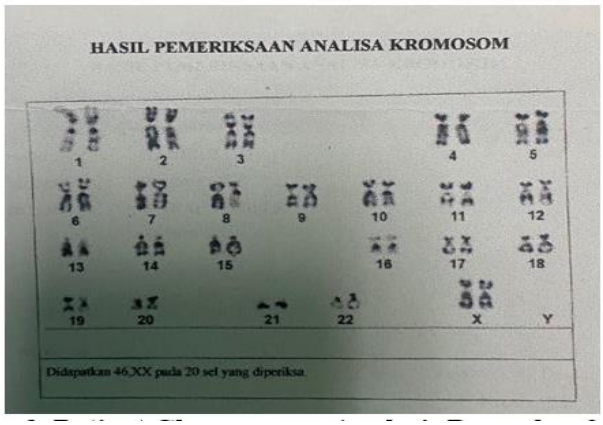


Figure 3. Patient chromosome analysis december 2021

On the examination of the thorax photo, a picture of the lungs and heart was obtained within normal limits.

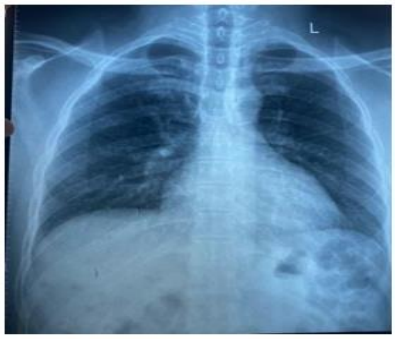


Figure 4. Thorax Photo *of* PA Position Patient October 2021

The results of the urogenital ultrasound examination on October 28, 2022, showed no stones, masses, or hydronephrosis on the right and left kidneys. There is no image of the masses and stones in the bullying. And it was found to resemble the uterus, prostate, cervix, and vagina in axial pieces.

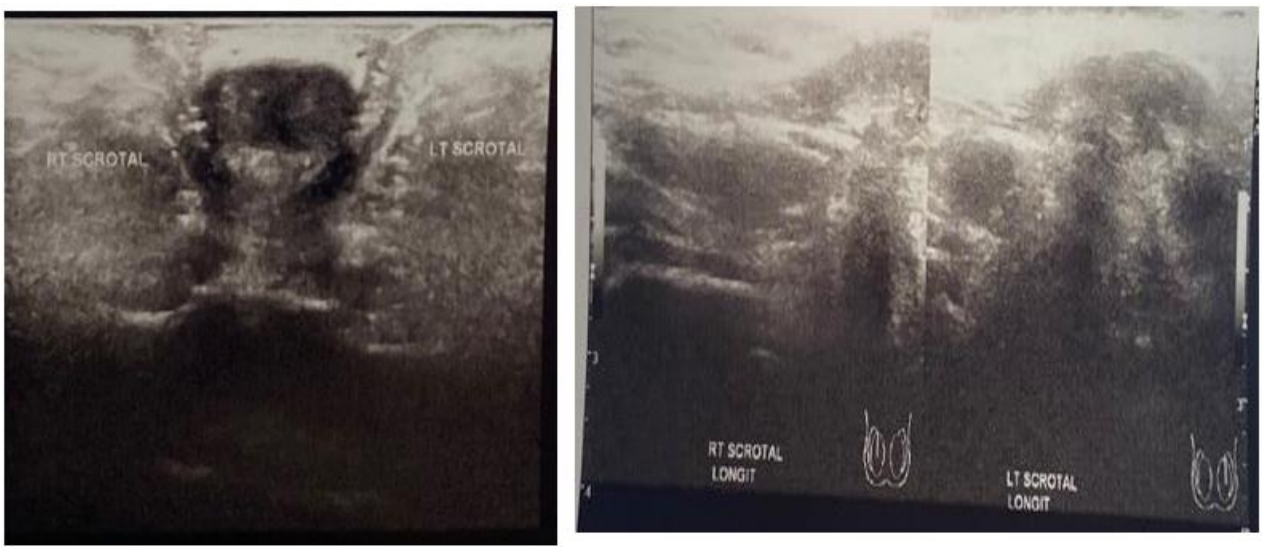


Figure 5. Uro genital ultrasound october 2021

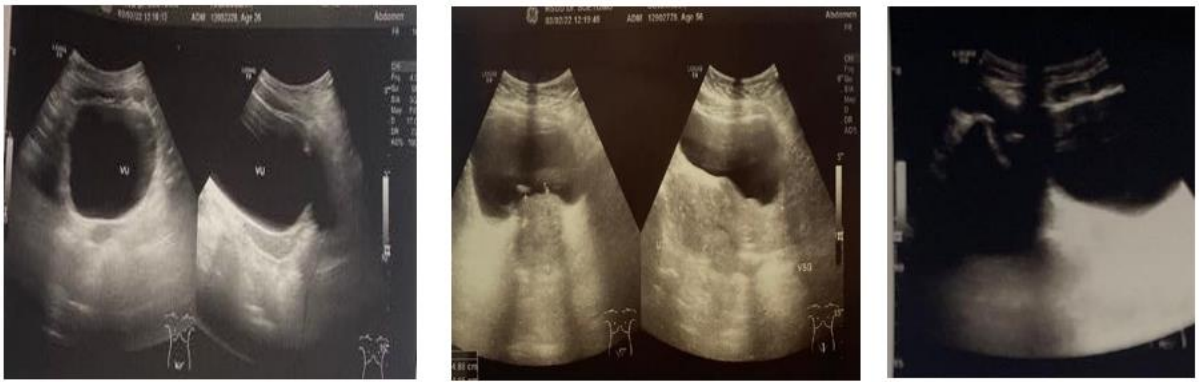


Figure 6. Uro genital ultrasound february 2022

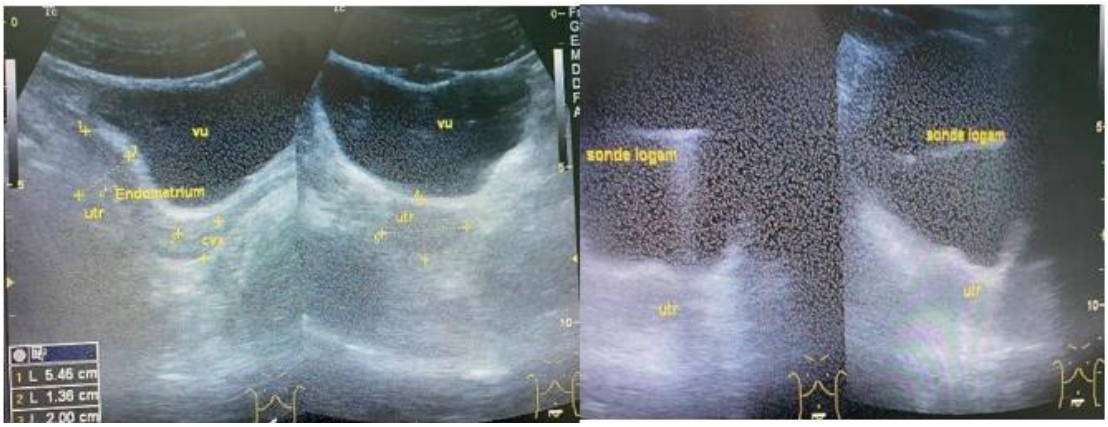
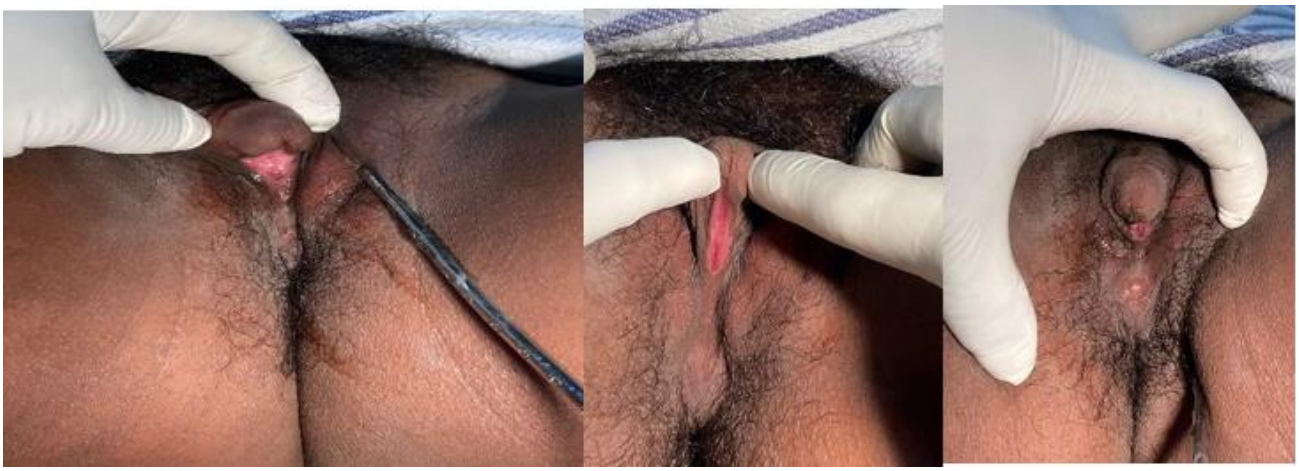


Figure 7. Urogenital ultrasound with marker sonde



Gambar 8. Mri Abdomen pelvis dengan kontras

The results of the pelvic abdomen MRI in March 2022 showed a formation resembling the uterus with an image of the endometrium line, accompanied by a picture of the vagina, the right and left ovaries, according to the rudimentary image of the female internal genitalia. A tubular formation that resembles a penis, without an image of the oue mouth in the distal part, can constitute a clitoromegaly. There is no image of the testicle in the pelvic cavity or abdominal cavity, and there is no image of the scrotum, seminal vesicle, or prostate, showing left adrenal hyperplasia.

Figure 9. Patient's contrast head CT-Scan results

In the patient, a CT scan of the head without contrast has been carried out, and no abnormalities in the parenchyma of the brain have been found.

Discussion

Primary amenorrhea can be established if the patient is characterized by secondary sex characteristics but has not experienced *menarche* until the age of 16. Changes during puberty over 3 years can be measured using *Tanner Staging*. The normal development of puberty in a woman can be seen from the illustration in Figure 9 (Roberts, 2016).

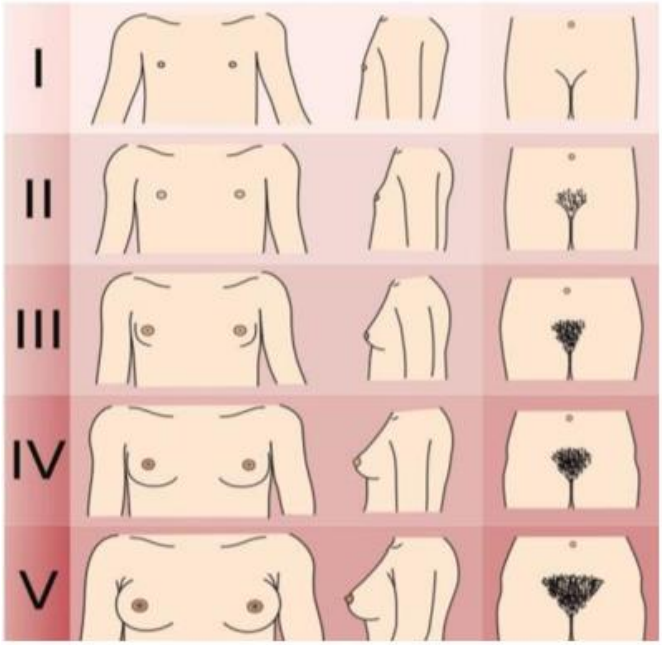


Figure 10

In this patient, criteria were found that met primary amenorrhea, where the patient had not *menarched* at the age of 16 years, which had been proven through chromosomal examination with a result of 46.XX, and there was a secondary sex, namely pubic hair, in accordance with Tanner 5. The breast growth of this patient does not represent secondary sex growth, according to Tanner 1, due to an increase in testosterone, so that it is competitive with estrogen to occupy receptors in the breast, so that breast growth in this patient is inhibited. One of the primary causes of amenorrhea to consider is congenital adrenal hyperplasia.

Congenital adrenal hyperplasia (HAK) includes a family of autosomal recessive disorders characterized by mild to acute symptoms of impaired cortisol synthesis due to a deficiency of one of the five adrenal steroidogenic enzymes required for cortisol production. Conventionally, HAK is divided into classic (KHAK), presented with a waste of salt or a simple form of virilization that is noticeably visible at birth and/or in the neonatal period, and non-classical (NKHAK), representing a less severe form of abnormality that has no genital ambiguity, a condition that is not directly life-threatening, appears later in life, shows no symptoms or can be a condition that is misdiagnosed as another disease. However, these limitations are not absolute, and the challenge at the moment is to consider HAK as a mild or severe phenotype spectrum, so that it is clear the direction of its management and management (Speiser *et al.*, 2010; Turcu and Auchus, 2015).

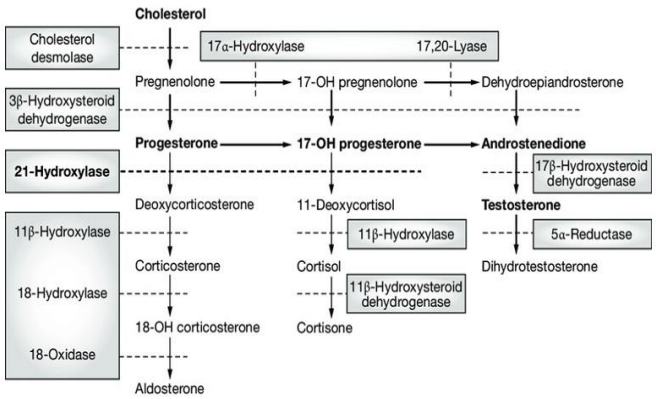
In this patient, an anamnesis was carried out, where the patient felt an abnormality in the shape of his penis and felt that there was a disturbance regarding erection. The patient never felt weakness, dizziness, muscle weakness, seizures, or fainting. Patients also said that eating and drinking were normal and never experienced excessive urination. The patient deliberately came for treatment because he wanted to get married and improve the shape of his penis.

From the height measurements, the patient was short when compared to the average height of women of her age. This is due to the faster closure of the epiphyseal plate as a result of high levels of sex steroids, ending with *glucocorticoid-induced inhibition of growth axis results.* From the physical examination, breasts were obtained according to Tanner 1 and pubic hair according to Tanner 5, and a vagina with a length of 5 cm was obtained (Speiser *et al.*, 2010).

Compared to the diagnosis of the classic form, which occurs at birth or during the neonatal period due to genital ambiguity and/or symptoms due to the loss of a lot of salt or through the most extensive screening programs in some countries, cases of NKHAK are not easy to detect (White, 2009; Gidlöf *et al.*, 2013). Basic clinical guidelines proposed by the Endocrinologist community recommend a baseline non-stimulation value of 17 OHPs as a screening tool for NCKAH. If in the morning the level of 17-OHP is more than 1.8 ng/mL in the menstrual follicular phase, further evaluation should be carried out immediately

because a figure above 1.8 ng/mL represents 90% of the population with NKKAH. Decreased blood cortisol levels, increased ACTH, free testosterone, androstenedion, DHEAS, and progesterone levels, and 17-OH are hallmarks of adrenal hyperandrogenism. Laboratory indicators for 21-hydroxylase deficiency should not exceed the reference value, represented by a 17-OH level of 10-100 ng/ml, which would confirm a KAH condition. (Azziz *et al.*, 1999; Moran *et al.*, 2000; Guarnotta *et al.*, 2020).

In this patient, amenorrhea occurs outside the axis of the hypothalamus, the pituitary pituitary of the ovaries. Ultrasound, abdominal and pelvic MRI, and head CT scan have been performed. From the ultrasound of this patient, the uterus and adnexa were found, and on the MRI, it was found that there were adrenal abnormalities, where there was an enlargement of the bilateral adrenal glands, while on the CT Scan examination, no abnormalities were found in the area of the pituitary gland. Then laboratory tests were carried out, namely DL, SGOT/SGPT, albumin, urea/creatinine, serum electrolytes (sodium/potassium/chloride), FSH, LH, estradiol, testosterone, 17-OHP, and GDA. All the laboratory results showed that there was an increase in testosterone, estradiol, and 17 OHP (53.29 ng/ml). Unfortunately, this patient did not undergo diagnostic laparoscopy and histo PA examination because the patient refused to undergo temporary surgery.



The Picture 11. Defective synthesis enzyme 21-hydroxylase (White, 2009)

The increase in 17-OHP in this patient is due to a deficiency of the enzyme 21-hydroxylase, where this enzyme is supposed to convert 17-OHP to 11-deoxycortisol and progesterone to deoxycorticosterone, resulting in high levels of 17-OHP in this patient. Thus, it is shown that the occurrence of primary amenorrhea in this patient is caused by non-classical Congenital Adrenal Hyperplasia (HAK).

Non-classical congenital adrenal hyperplasia (NKAH) or slow-onset due to 21-hydroxylase deficiency is one of the most common autosomal recessive disorders. The reported prevalence is about 1 in 1000. Affected individuals usually present with signs and symptoms of excess androgens. NKAH treatment needs to be directed at the symptoms. For affected children, treatment goals include normal linear growth rate, normal bone maturation rate, and "timely" puberty. For affected adolescent and adult women, treatment goals include regular menstrual cycles, prevention or development of hirsutism and acne, and fertility. Treatment should be individual and should not be started just to lower the concentration of abnormally increased hormones (Witchel, 2013).

In this patient, there are no symptoms that show signs of adrenal and/or other hormonal crises that require immediate therapy. Patients are also still rethinking the steps to be taken related to their gender preferences. From the approach of medical discussion, it was decided that therapies related to penile reconstruction and hormone replacement would be decided further once the patient was confident in his choice. Unfortunately, until now, the patient has never returned and is difficult to contact.

Conclusion

46. XX KAH is a rare case. Patient management is based on substantial examination, and patient preferences play an important role in determining the type of treatment. In this case, the entire examination (physical, laboratory, karyotype, radiology, and endourology) corresponds to the diagnosis of KAH, and the patient is categorized as suffering from simple virilized KAH due to the absence of classic symptoms. The patient tends to identify himself as a man, so that a penile reconstruction will be carried out if the multidisciplinary team approves, and the patient will be adapted to be a man.

Daftar Pustaka

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