

Simple Virilization Type of Classic Congenital Adrenal Hyperplasia: Case Report

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We have reported a case of 21 year old patient with congenital adrenal hyperplasia that manifested with ambiguous genitalia and other signs of androgen excess. Chromosome analysis revealed 46 XX. Laboratory examination and imaging showed high level of 17-hydroxyprogesterone, undeveloped uterus, two ovaries with follicles, no testicles, no prostate, and mass at upper side of both kidney with irregular border confirmed the diagnosis. It was planned to give glucocorticoid therapy to the patient to suppress androgen level, genital reconstruction surgery and psychosexual therapy to reared as a woman, but she refused all suggestions because she wanted to be considered a man.

Keywords: Congenital Adrenal Hyperplasia, Androgen excess, Glucocorticoid therapy, Genital reconstruction.

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive genetic disorders. CAH is caused by deficiency of enzymes needed in adrenal steroid biosynthesis, this will result in increased production of adrenocorticotrophic hormone (ACTH) and will further enlarge the adrenal gland. According to Office of Rare Diseases (ORD) from National Institutes of Health (NIH), CAH is a rare disorder, in United States of America the incidence is less than 200.000 of

total population. Indonesia recorded 292 patients with CAH from 2009-2014, this data was gained by pediatric endocrinologists because no case has been detected in adult patients¹.

Case Report

Patient was a 21 year old, a Balinese, unmarried, consulted from Obstetric and Gynecology Department with *ambiguous genitalia*. Her urine flows from her women's part of her genital, and she wanted to be able to urinate in

standing position like a man. She has always felt that she is a man, but her family treated her as a girl since she was born. During childhood she had taller figure compared to her friends, but her growth has been slowed down since adolescence. She also easily got pimples on her face. She had never ejaculated and also has never gotten menarche. Agreement to do and take picture of physical examination especially genital examination were given by herself. Physical examination revealed short stature 133 cm, normal vital signs, tanner I breasts, penile gland-like enlarged clitoris with 5x2 cm in size. There was no hymen found from rectal touch examination. Urethra was under the clitoris, the labia majora looked like scrotum, testicles were unpalpable, and there was vagina, 4 cm depth from vaginal sondage examination. Speculum examination cannot be performed because of the small size of vagina.

Laboratory examination revealed increase in 17-Hydroxyprogesterone (743.53 ng/dL), increase in dehydroepiandrosterone sulfate 667 mcg/dL (80-350 mcg/dL), normal range for testosterone and estradiol, decrease in follicle stimulating hormone 4.85 mIU/mL (5-20 mIU/mL), decrease in luteinizing hormone 1.45 mIU/mL (5-20 mIU/mL), and patient's chromosome analysis result was 46 XX.

Trans abdominal ultrasonography and computed tomography showed undeveloped uterus, two ovaries with follicles, no testicles, no prostate, and mass at upper side of both kidney with irregular border.

We assessed this patient with congenital adrenal hyperplasia simple virilization type,



Fig. 1. Picture of the patient

primary amenorrhea, bilateral adrenal tumour probably myelolipoma, and transexualism. Our multi discipline team decided to keep the female identity of the patient with glucocorticoid, hormonal therapy, genital reconstruction, and supportive psychotherapy. However the patient refused our recommendation because she still wanted to be identified as male.

DISCUSSION

CAH is a group of autosomal recessive genetic disorders. CAH caused by deficiency of enzymes needed in adrenal steroid biosynthesis; 21-hydroxylase, 11 β -hydroxylase, 17 α -hydroxylase, 3 β -hydroxysteroid dehydrogenase or P450 oxidoreductase.^{2,3}

21-hydroxylase enzyme deficiency is the most common cause of CAH (90-95%).^{2,3,5} 21-hydroxylase turns 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone, a precursor of cortisol and aldosterone.^{2,3} Steroidogenesis process in CAH can be viewed in picture 6. Failure of cortisol synthesis will increase ACTH from anterior pituitary and causes adrenal hyperplasia.^{6,7}

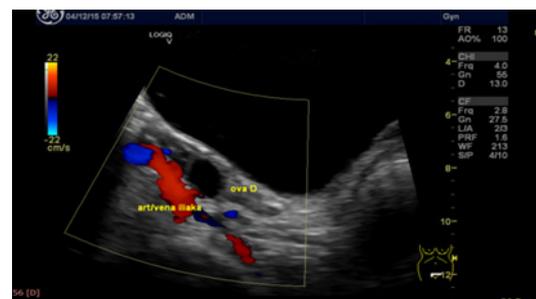
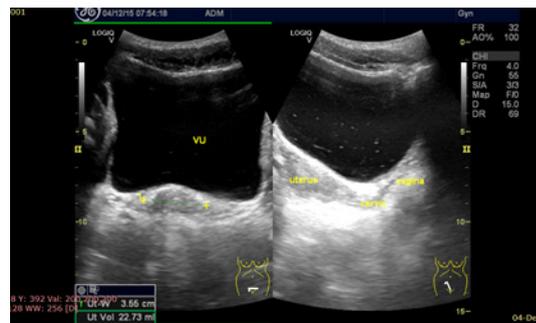


Fig. 2. Trans abdominal ultrasonography examination. Vagina, cervix, uterus (upper picture), and right ovarium (lower picture)

There are two types of CAH, classic and non classic. The classic type consist of salt wasting type (75%) and simple virilization type (25%). In salt wasting type, there is no 21-hydroxylase, so both aldosterone and cortisol synthesis will be disrupted . In simple virilization type, a small part of the enzyme still can function normally so disruption only happens in cortisol synthesis.^{8,9}

Clinical manifestations in CAH are caused by cortisol and aldosterone deficiency and excess of androgen production. Hormonal examination can help us to differentiate type of CAH, but the gold standard is molecular genetic analysis^{2-5,10}

In our case clinical manifestations are caused by androgen excess, such as short stature, ambiguous genital, acne, and amenorrhea. Our patient didn't have hirsutism though, this can be caused by insensitivity of hair follicle to androgen, so the pilosebaceous unit differentiate to sebaceous gland.^{11,12,13}

Treatment goals for CAH in adults are

to prevent side effect from long term adrenal replacement therapy and to keep patient's fertility.^{5,10,14,17} Modalities used in treatment can be seen at table 3. The corner stone of CAH treatment is glucocorticoid; hydrocortisone (15-45 mg/day) , prednisone (5-7.5 mg/ day), and dexamethasone (0.25-0.5 mg/day),^{9,10,12-15}

Fertility impairment in CAH cannot be treated only by steroid but also surgery for genital reconstruction and psychosexual therapy. Our

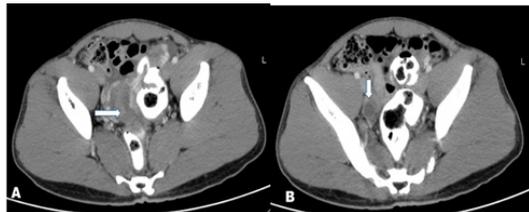


Fig. 3. Contrast CT scan abdomen showed undeveloped uterus and right ovarium

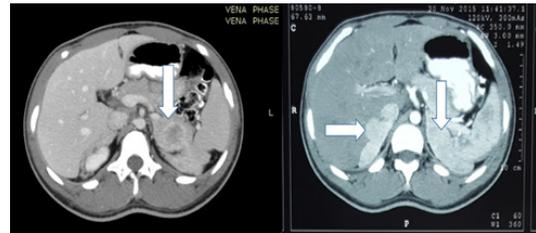


Fig. 4. Contrast CT scan abdomen showed bilateral upper kidney mass

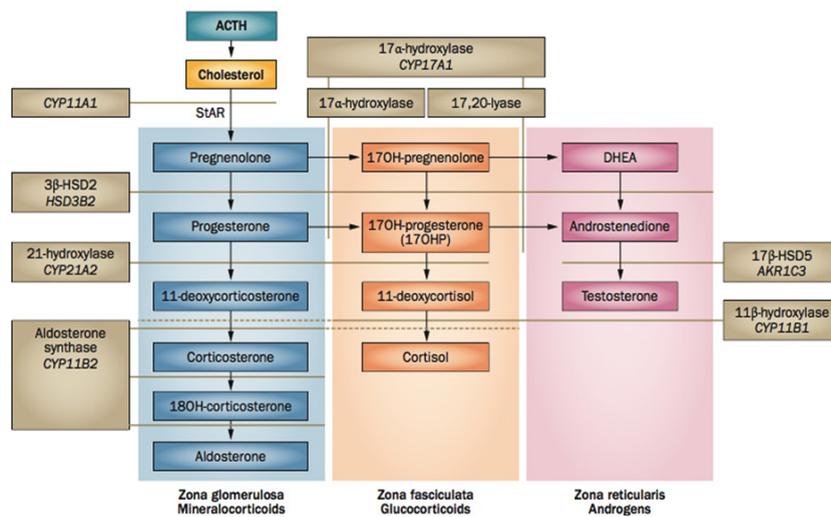


Fig. 5. Adrenal steroidogenesis process⁴

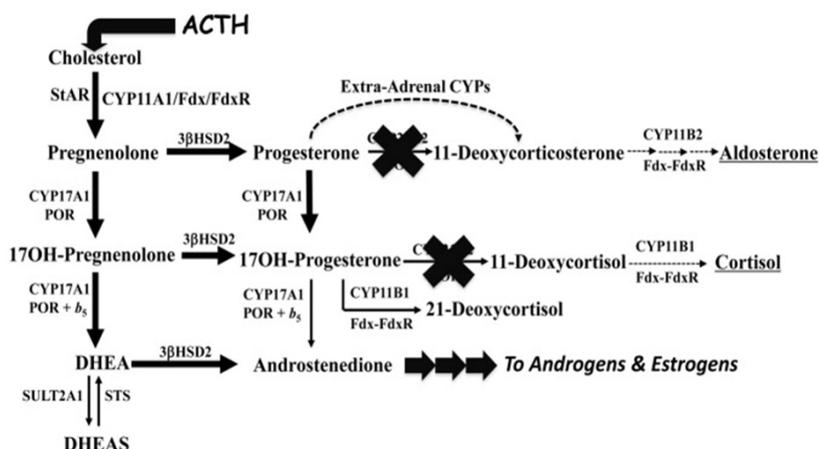


Fig. 6. Steroidogenesis in CAH caused by 21-hydroxylase enzyme deficiency³

patient refused the treatment recommendation to suppress androgen because she wanted to be identified as a man and wanted to do genital reconstruction surgery to be a man. Our team refused her request because currently there is no legal law about gender changing in Indonesia. Abundant androgen exposure since intrauterine period was very likely that contributed to her desire to be a man.

One of the complication from CAH is adrenal gland tumor, usually detected accidentally during imaging examination. This tumor is caused

by long term high ACTH exposure. Our patient had non contrast enhancement tumor from her imaging, so we assumed that her tumor is myelolipoma.

CONCLUSION

We have reported case of patient with congenital adrenal hyperplasia that manifested in ambiguous genitalia and other signs of androgen excess. Although chromosome analysis revealed 46 XX, patient has always identified herself as a man because of her high level of androgen. Laboratory

Table 1. Clinical and hormonal manifestation in CAH¹¹

Manifestation	CAH type					
	Salt Wasting		Simple Virilization		Non classic	
	Male	Female	Male	Female	Male	Female
Age when diagnosed	Neonatus-6 month	Neonatus-1 month	2 - 4 year	Neonatus-2 year	Children-	adults
External genital	Normal	Ambi-guous	Normal	Ambi-guous	Nor-mal	Normal/clitormegaly
Aldosterone	Low	Normal	Normal			
Renin	High	Normal/increased	Normal			
cortisol	Low	Low	Normal			
17-OHP	> 20.000 ng/dL	10.000 – 20.000 ng/dL	ACTH Stimulation: 1500 -10.000 ng/dL			
21-hydroxylase enzyme activity	0	1 - 10%	10-75%			

Table 1. Medication used in CAH¹²

	Physiologic effects	Clinical effects	Side effects
Glucocorticoid	Cortisol replacement therapy; suppressing hypothalamus-pituitary-adrenal axis to decrease adrenal androgen secretion.	Adrenal insufficiency therapy, prevention of virilization in women, treatment and prevention of infertility.	Iatrogenic cushing syndrome.
Fludrocortisone	Mineralocorticoid replacement therapy; suppressing renin-angiotensin-aldosterone axis, decreasing vasopressin, ACTH, and adrenal androgen secretion.	Keeping sodium and potassium balance, prevention of intravascular fluid depletion, decrease glucocorticoid dose.	Hypertension.
Contraception pill	Decrease serum androgen, suppressing hypothalamus-pituitary-adrenal axis to decrease ovarium androgen.	Regulate menstruation cycle, decrease hirsutism.	-
Spironolactone	Mineralocorticoid antagonis; competitive inhibitor of androgen receptor; inhibit 5 α -reductase therefore decreasing androgen production.	Decrease hirsutism.	Diuresis.

examination and imaging which resulted in high level of 17-Hydroxyprogesterone, undeveloped uterus, two ovaries with follicles, no testicles, no prostate, and mass at upper side of both kidney with irregular border confirmed the diagnosis. Patient was planned to be given glucocorticoid therapy to suppress androgen level, genital reconstruction surgery and psychosexual therapy to be a woman, but she refused all suggestions because she wanted to be a man.

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