CLASSIC SIMPLE VIRILIZING CONGENTAL ADRENAL HYPERPLASIA IN A THREE YEARS OLD GIRL

Alice Indradjaja, I Wayan Bikin Suryawan, I Made Arimbawa

Department of Child Health Udayana University Medical School / Sanglah Hospital Denpasar

ABSTRACT

Congenital adrenal hyperplasia (CAH) refers to a group of genetic enzyme deficiencies that impair steroid synthesis by the adrenal cortex. The most common form is 21-hydroxylase deficiency (21 OHD), accounting for more than 90% of the cases. The fundamental defect among patients with CAH due to 21-hydroxylase deficiency is that they cannot adequately synthesize cortisol. Classic 21-hydroxylase deficiency in female newborn cause virilized external genital. We reported a case of classic simple virilizing CAH in a three years old girl. The patient came to the pediatric outpatient clinic at Sanglah hospital with chief complaint of about having enlarged clitoris, clitoris patient to appear enlarged and elongated progressively resembling genitals boys and accompanied the growth of public hair. She was born with ambiguous genitalia. She was very active compared to children her age, behaves in boyish manner and looked darker-skinned. She was diagnosed with 21-hydroxylase deficiency based on a 17-OH-progesterone level of >1,200 ng/dl. Prader staging and virilization of genitalia eksterna was stage III. On bone age examination revealed and advanced bone age, USG abdomen was normal and result of chromosome analysis was 46,XX. She had never salt-losing adrenal crises during the first 3 years of life and genital surgery was performed at 3 years old. The patient was given counseling, regular monitoring and was planned to receive hydrocortisone therapy. Prognosis of the patient was good. [**MEDICINA 2014;45:58-64].**

Keywords *: classic simple virilizing, congenital adrenal hyperplasia*

HIPERPLASIA ADRENAL KONGENITAL (HAK) KLASIK *SIMPLE VIRILIZING* PADA ANAK UMUR 3 TAHUN

Alice Indradjaja, I Wayan Bikin Suryawan, I Made Arimbawa

Bagian Ilmu Kesehatan Anak Fakultas Kedokteran Universitas Udayana / Rumah Sakit Umum Pusat Sanglah, Denpasar

ABSTRAK

Hiperplasia adrenal kongenital merupakan salah satu dari kelompok kelainan genetik akibat defisiensi enzim yang diperlukan untuk biosintesis steroid di korteks kelenjar adrenal. Bentuk kelainan hiperplasia adrenal kongenital yang tersering adalah defisiensi enzim 21-hidroksilase (21 OHD) hingga mencapai 90% kasus. Kelainan utama pada pasien dengan defisiensi enzim 21-hidroksilase adalah kegagalan sintesis kortisol secara adekuat. Defisiensi 21-hidroksilase klasik tipe virilisasi sederhana menyebabkan genitalia ambigu pada bayi perempuan. Dilaporkan sebuah kasus hiperplasia adrenal kongenital klasik tipe virilisasi sederhana pada anak perempuan usia tiga tahun. Pasien dirujuk ke Poliklinik anak RSUP Sanglah Denpasar dengan keluhan utama pembesaran dan pemanjangan klitoris yang progresif disertai tumbuhnya bulu pubis. Pasien lahir dengan genitalia ambigu. Pasien didiagnosis defisiensi 21-hidroksilase berdasarkan hasil pemeriksaan kadar progesteron 17-OH >1.200ng/dl dan pemeriksaan fisik didapatkan prader derajat III. Pada pemeriksaan usia tulang menunjukkan usia tulang yang melebihi umurnya, USG abdomen dalam batas normal dengan hasil analisis kromosom 46,XX. Pasien tidak pernah mengalami krisis adrenal selama 3 tahun dan menjalani tindakan pembedahan pada usia 3 tahun. Keluarga pasien diberikan konseling, dilakukan monitor berkala pada pasien dan terapi hidrokortison. Prognosis pada pasien ini baik. [**MEDICINA 2014;45:58-64].**

Kata kunci: *virilisasi tipe klasik, hiperplasia adrenal kongenital*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) refers to a group of genetic enzyme deficiencies that impair normal steroid synthesis by the adrenal cortex. The most common form is 21 hydroxylase deficiency (21 OHD), accounting for more than 90% of the cases. Congenital adrenal hyperplasia caused by 21-hydroxylase deficiency is an autosomal recessive condition, in which deletions or mutations of the cytochrome P450 21-hydroxylase gene result in glucocorticoid and often mineralocorticoid deficiency.[1]

Screening studies indicate that the worldwide incidence of classical 21 OHD is 1:15,000 to 1:16,000 live births, 1-3 of which approximately 75% are salt wasters. The worldwide incidence of NCCAH is much higher at 1:1000, with a frequency as high as 1:27 among Ashkenazi Jews.[1]

The cortisol synthetic block leads to corticotropin stimulation of the adrenal cortex, with accumulation of cortisol precursors that are diverted to sex hormone biosynthesis. A cardinal feature of classic or severe virilizing CAH in newborn females is genital ambiguity. If the disorder is not recognized and treated, both girls and boys undergo rapid postnatal growth and sexual precocity or, in the case of severe enzyme deficiency, neonatal salt loss, and death.[2]

The goal of therapy in CAH is to both correct the deficiency in cortisol secretion and suppresses ACTH overproduction. Proper treatment with glucocorticoid reduced stimulation of the androgen pathway, thus preventing further virilization and allowing normal growth and development. Treatment efficacy reflects the adequacy of adrenocortical suppression and is assessed by monitoring annualised growth velocity, the rate of skeletal maturation, and serum concentrations of androgen precursors.[2] In this report, we present a case of classic simple virilizing congenital adrenal hyperplasia and an overview of its management in the medical literature.

CASE ILLUSTRATION

BANM, a three year old girl, Balinese girl was referred from a pediatric endocrinologist to pediatric and urology outpatient clinic of Sanglah Hospital on May 15th, 2012 with chief complaint of about having enlarged clitoris. Pediatrician who involved in this child noted congenital abnormality in the child, and parents were suggested to start initial therapy for their daughter as soon as possible. She got hydrocortisone oral for six month but it was stoped by her family and continued to have alternative treatment. Since 1 year, patient clitoris started to enlarged and elongated progressively resembling genitals boys. That complaint were accompanied by pubic hair appears since 2 weeks before she brougth to pediatric outpatient clinic. Hair growth was not found elsewhere and there was no pimples. She did not get a menarche. The parents said she was very active compared to children her age, behaves in boyish manner "tomboy" and had dark colour skin as shown in **Figure 1**. There was no repeated vomiting, dehydration or extreme muscle weakness.

Family history of ambiguous genitalia was denied. There was no history of therapy hormonal and genetic abnormalities in the family. There was no family relationship between the father and the mother.

Physical examination revealed an alert girl, who looked very active. The pulse rate was 98 times per minute and regular, respiratory rate was 20 times per minute, axillary temperature was 36.8°C, blood pressure was 90/60 mmHg. Her body weight was 16 kilogram (P90 CDC 2000) with body height was 108.5 centimetre (P90 CDC 2000) and Waterlow status was 88%. Head circumference was 48.5 centimetre (between -2SD and 2 SD). The height of upper segment (US) was 56 centimetre and height lower segment was 50 centimetre (LS), ratio US/LS was 1.12. The length of arm span was 10.9 centimetre. Her mother's height was 152 centimetre, meanwhile her father's height was 158 centimetre. The mid-parental height was 155.25 centimetre tall and range high of potential genetic her parent was 140.25-157.25 centimetre.

Figure 1. The patient with hyperpigmentation and masculinity.

The hair was fine and black. No dysmorphic picture. The conjunctiva was not anemic or icteric, and the pupil reflexes were normal. Facial appearance : mustache had not grown. Hyperpigmentation of the skin. The sound had not changed.

The chest examination revealed to precordial bulging. Ictus cordis was palpable on the 5th intercostals space on the left midclavicular line. There were no thrill and no RV heave. On auscultation, the first and second heart sounds were normal, without murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The

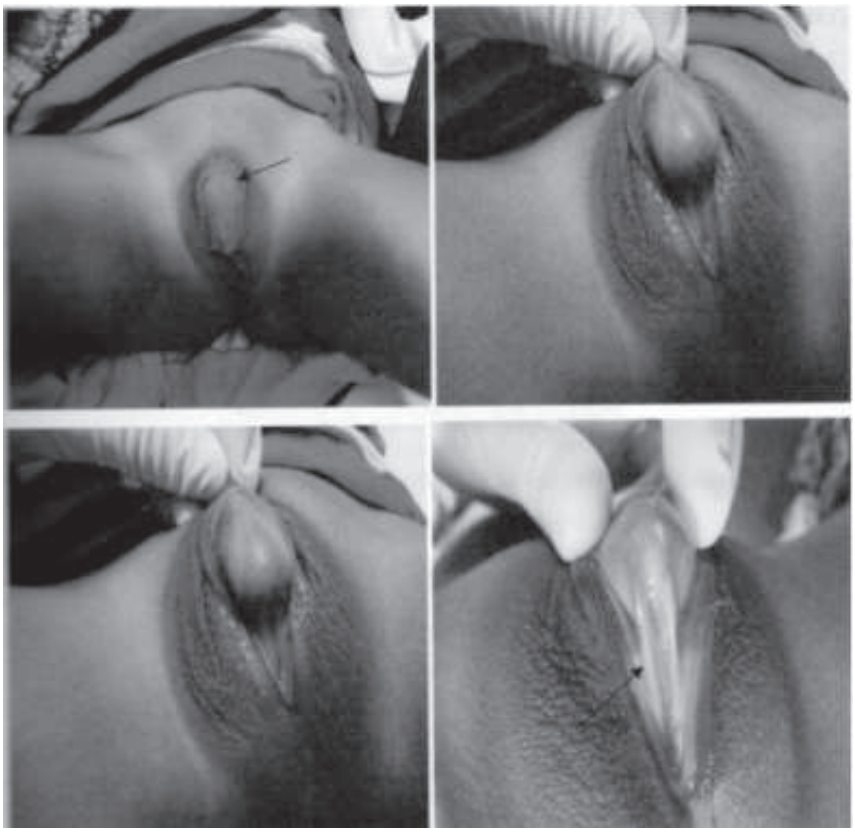

Figure 2. Ambiguous genitalia in patient: clitoromegaly, public hair, labia dekstra and sinistra look like scrotal skin without testicular volume.

abdomen was not distended. Bowel sounds was normal. Both liver and spleen were impalpable. There was no tenderness in the epigastrium area and nowhere else. There were no signs of ascites. There were also no palpable or visible masses. The palpable tone of the abdomen was soft, no musculary tightness.

Prader staging and virilization of genitalia eksterna was stage III. Urogenitalia : flank area no buldging and no ballottement, genitalia externa was virilitation with phallus length 4 centimetres, orificium urethra eksterna below the clitoris, labia dekstra and sinistra look like scrotal skin, without testicular volume dekstra and sinistra and public hair as shown in **Figure 2**.

We planned for further examination such as complete blood count, electrolyte serum, blood sugar, cortisol serum, 17-OH progesterone, abdominal ultrasound, radiologic examination, and chromosomal analysis.

Laboratory data included a complete blood count of WBC 8.61 k/mL (54.5% neutrophils, lymphocytes 30.4%, monocyte 4.6%, eosinophil 7.0%; basophil 2.2%), Hb 11.6 g/dL; and Plt 576 k/mL. Hormon of 17-OH progesterone was >1200 mg/dl (normal <100ng/dl), blood sugar 74 mg/dl, sodium 140 mmol/L, pottasium 4.1 mmol/L, morning corticol serum 3.34 and afternoon corticol serum 6.48. Radiologic examinations revealed advance bone age similar to 6 years and 10 months old. The chest x-ray shown normal, IVP shown normal. Abdominal ultrasound : there was hollow structure at pelvic cavum was posterior from urinary vesica, suspected uterus (did not seem adrenal and ovarium tumor).

Results of chromosome analysis (June, 5th 2012) : samples were derived from peripheral blood heparin, 20 cells have been studied for the chromosomes with the application of G-banding technique and the number of chromosomes in each cell was 46, XX. There was no major structural abnormality.

Based on the clinical manifestation, laboratory findings, radiologi imaging, and chromosom analysis, the patient was then diagnosed with classic simple virilizing CAH and 46, XX disorder of sex development.

On October 9th 2012, the patient visited to Sanglah Hospital pro cystocopy reduction and clitoroplasty. Penectomy and clitoplasty done on October 11th 2012, shown in **Figure 3**. Corticosteroid for stress therapy before the surgery was given 24 hours before the surgery. A Glucocorticoid used was methylprednisolone. Hydrocortisone replaced by methylprednisolon becaused preparat was not available. Twenty four hours and 12 hours before surgery patient was take 4 mg methylprednisolone oral, 1 hour before surgery she got 10 mg methylprednisolone intravena and continue with 6 mg

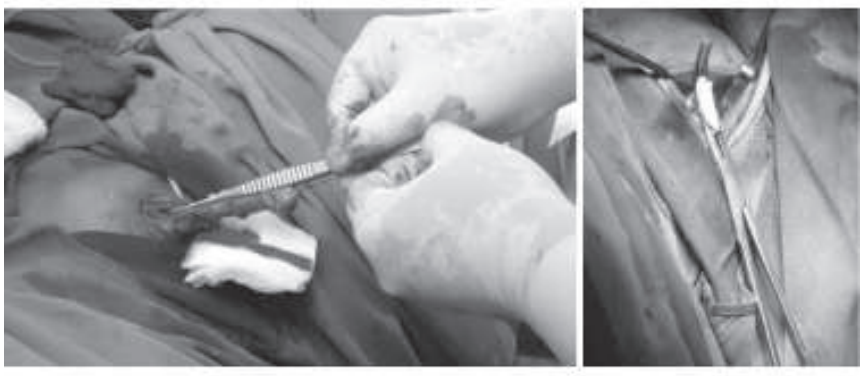

Figure 3. Penectomy and clitoplasty procedure.

methylprednisolone during surgery. The first day postoperative she got 5 mg methylprednisolone eight time a day intravena. The second day post operative she got 2.5 mg methylprednisolone eigth times a day and the third day after surgery she got 2mg-2mg-4mg methylprednisolone oral. The fourth day after surgery she got 1mg-1mg-2mg methylprednisolone oral and the continue with maintenance doses 10-15 mg/m2/day of methylprednisolone divided into 3 daily doses (2.5mg methylprednisolone three times a day). After that treated she could be outpatient.

DISCUSSION

Congenital adrenal hyperplasia is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. The incidence ranges from 1:10,000 to 1:15,000 births. The most common form of CAH is caused by 21-hydroxylase deficiency (90%).[2] Congenital adrenal hyperplasia owing to 11b-hydroxylase deficiency (11b-OHD) is the second most common cause of CAH, accounting for 5-8% of all cases.[3] The fundamental defect among patients with CAH due to 21-hydroxylase deficiency is that they cannot adequately synthesize cortisol. Inefficient cortisol synthesis signals the hypothalamus and pituitary to increase CRH and ACTH, respectively. Consequently, the adrenal glands become hyperplastic. But rather than cortisol, the adrenals produce excess sex hormone precursors that do not require 21-hydroxylase for their synthesis. Once secreted, these hormones are further metabolized to active adrogens-testosterone and dihydrotestosterone-and to a lesser extent estrogens-estrone and estradiol.[4]

Adrenal steroidogenesis occurs in three major pathways : glucocorticoids, mineralocorticoids, and androgen. These take place in different areas of the adrenal cortex : glucocorticoids (particularly cortisol), androgens, and estrogens in the zona fasciculata and reticularis; and aldosterone in the zona glomerulosa. These pathways serve as the basis for understanding the different forms of CAH. Adrenocorticotropic hormone (ACTH) regulates adrenal steroid production via a rate-limiting step that results in

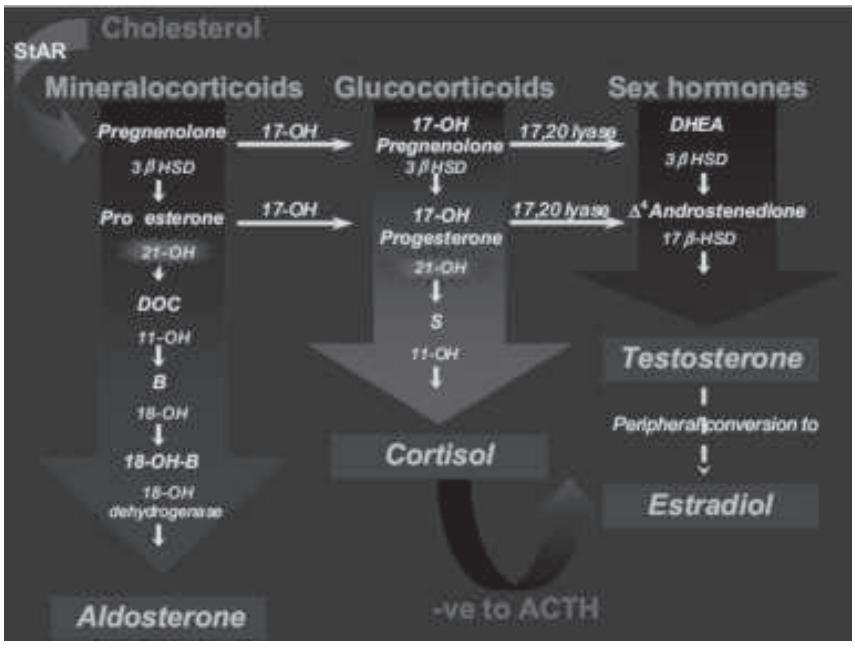

Figure 4. Illustrated adrenal steroidogenesis.[3]

pregnenolone, the principal substrate for the steroidogenic pathway as shown in **Figure 4**.[3,4]

Virilizing CAH is the most common cause of genital ambiguity, and 90-95% of CAH cases are caused by 21-hydroxylase deficiency. About three-quarters of patients cannot synthesize sufficient aldosterone to maintain sodium balance and are termed "salt wasters". This predisposes them to episodically develop potentially life-threatening hyponatremic dehydration.[5] Characteritics of different clinical forms of 21-hydrosilase deficiency are shown in **Table 1**.

Adrenal secretion of excess androgen precursors does not significantly affect male sexual differentiation. In females affected with CAH, however, the urogenital sinus is in the process of septation when the fetal adrenal begins to produce excess androgens; levels of circulating adrenal androgens are apparently sufficiently high to prevent formation of separate vaginal and urethral canals. Females with classical 21-OHD and 11b-hydroxylase deficiency CAH generally present at birth with masculinization of their genitalia. Adrenocortical function begins around the 7th week of gestation; thus, a female fetus with classical CAH is exposed to adrenal androgens at the critical time of sexual differentiation (approsimately 9 to 15 weeks gestational age).[6] Androgens interact with the receptors on genital skin and induce changes in the developing external female genitalia. This leads to clitoral enlargement, fusion and scrotalization of the labial folds, and rostral migration of the urethral/vaginal perineal orifice, placing the phallus in the male position. However internal Wolffian structures, such as the prostate gland and spermatic ducts, are usually not virilized, premumably because development of the Wolffian ducts requires markedly higher focal

Table 1. Characteritics of different clinical forms of 21-hydrosilase deficiency[5]

Phenotype	Classic salt wasting		Classic simple virilizing		Nonclassic	
	♂	♀	♂	♀	♂	♀
Age at diagnosis	Newborn-6m	Newborn-1m	2-4y	Newborn-2y	Child-adult	Child-adult
Genitalia	Normal	Ambigous	Normal	Ambigous	Normal ↑clitoris	+/-
Aldosterone	↓		Normal		Normal	
Renin	↓		May be ↑		Normal	
Cortisol	↓		↓		Normal	
17-OH-progesterone	>20,000 ng/dl		>10,000-20,000ng/dl		1,500-10,000ng/dl	
Testosterone	↑ In puberty only	↑	↑ In puberty only	↑	Variably ↑ in Puberty only	Variably ↑
Treatment	Glucocorticoid + mineralocorticoid (+sodium)		Glucocorticoid (+ mineralocorticoid)		Glucocorticoid, if symtomatic	
Somatic growth[a]	-2-3 SD, husky-obese		-1-2 SD		?-1 SD	
Incidence[b]	1/20,000		1/60,000		1/1000	
Typical mutation	Deletion Large convertion Nt 656g ("intron 2 g") G1108Δnt 1236N/V237E/M239K Q318X R356W		I172N nt 656g		V281L P30L	
% Enzymatic activity	0		1		20-50	

[a]SD,Standard deviation scores.
[b]Incidence in general white population.

concentrations of testosterone than the external genitalia. The degree of genital virilization may range from mild clitoral enlargement alone to, in rare cases, a penile urethra. Degrees of genital virilization are classified into five Prader stage shown in **Figure 5**.[5,6]

In our case, the patient was born with ambiguous genitalia. She was diagnosed 21-hydroxylase deficiency based on a 17-OH-progesterone level of>1,200 ng/dl (<100 nmol/liter). At approximately 2 years old she had abnormality of enlargement clitoris, public hair, skin hiperpigmentation, and masculinity. Prader staging and virilization of genitalia eksterna is stage III. Genitalia externa was virilitation with phallus length 4 centimeters, orificium urethra eksterna below the clitoris, labia dekstra and sinistra look like scrotal skin, without testicular volume dekstra and sinistra. The results of ultrasound imaging examination showed hollow structure at pelvic cavum was posterior from urinary vesica, suspected uterus whereas the results of chromosome analysis showed that the number of chromosomes in each cell of studied were 46, XX. Radiologic examinations revealed advance bone age similar to 6 years and 10 months old.

The treatment of CAH patients requires an appropriately trained multidisciplinary team. Every couple that has a child with ambiguous genitalia must be assessed and receive counselling by an experienced psychologist, specialized in gender identity, who must act as soon as the diagnosis is suspected, and then follow the family periodically, more frequently during the periods before and after genitoplasty. Parents must be informed by the physician and psychologist about normal sexual development. In our case, the patient was treated by a team which consists of endocrinologist pediatric, pediatric urologic surgeon, plastic surgeon, a psychologist.

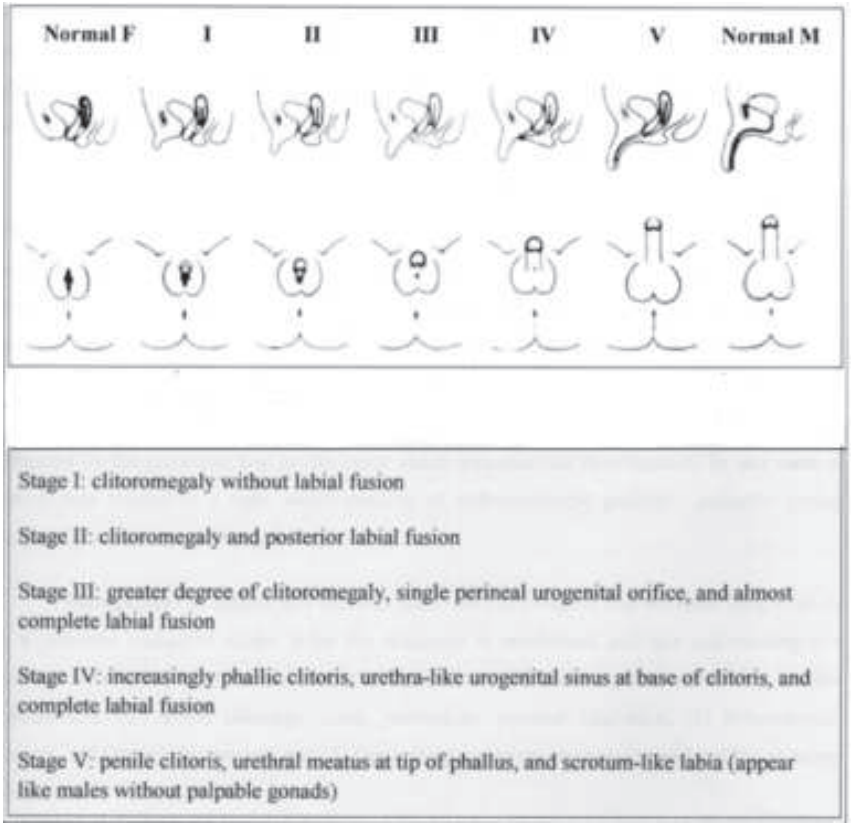

Figure 5. Different degrees of virilization according to the scale developed by Prader.[5,6]

Management of infants and children with CAH is complex and warrants long term care. After the diagnosis is confirmed, major management issues include : (1) Initiating and monitoring hormone replacement; (2) Stres coverage, crisis prevention, parental education; (3) Reconstructive surgery; (4) Optimizing growth, and (5) Optimizing androgen suppression and fertility in women with CAH.[7]

The primary goals of hormone replacement are to protect from adrenal insufficiency and to suppress the excessive adrenal androgen production. The optimal glucocorticoid dose replaces deficient endogenous cortisol, prevents virilization, optimizes growth, and protects fertility. The normal daily production rate of cortisol is approximately 6 mg/m2/day; however, doses of 12 to 15 mg/m2/day or higher are tyipicall needed to adequately reduce androgen overproduction.[7] The Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology have stated that the optimal glucocordicoid dosing for children is 10-15 mg/m^2/day of hydrocortisone divided into 3 daily doses, with doses as high as 25mg/m2 during infancy. Treatment with hydrocortisone, prednisone, or dexamethasone can result in normal growth if therapy is initiated before the bone age advances beyond chronological age.[9] At the completion of linear growth, the consensus statement gives the option of changing to prednisolone 2-4 mg/m2 twice daily or dexamethasone 0.25-0.375 mg/m2 once daily. Fludrocortisone is the only pharmaceutically available mineralocorticoid and is usually used in doses of 0.1 to 0.2 mg daily.[10]

In this case, the patient was started on hydrocortisone oral since she diagnosed as CAH (3 days old) for six month but was stoped by her family for 2 years.

Patients with severe forms of 21-hydroxylase deficiency are unable to produce a sufficient cortisol response to physical stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma, and therefore require increased doses of glucocorticoid during such episodes. Glucocorticoid needs are increased during illness and stress, and missed doses during an illness such as the "flu" (or viral gastroenteritis) can lead within hours to reduced blood pressure, shock, and death. Maintenance doses should be resumed when the patient is stable.[10]

In our case, the patient never experienced salt-losing adrenal crises during the first 3 yr of life but at approximately 2 years old she had abnormality of enlargement clitoris, public hair, skin hiperpigmentation, and masculinity. Genital surgery was performed at 3 years old. She was taken corticosteroid for stress therapy before the surgery (Guidelines from Departement of Child Health, Medical Faculty of Indonesia University, Cipto Mangunkusumo General Hospital, Jakarta, endocrinologist division).

Surgical reconstruction of abnormal genitalia has been offered to parents of severaly virilized girls with CAH since the first half of the 20th century. In recent guidelines, it is suggested that in severe cases (Prader stage C3), clitoral and vaginal surgery can be considered in incfancy. Genital surgery between 2 and 6 months of age is considered the standard of practice for the virilized classic CAH female. The aims of surgical treatment are to allow development of adequate external genitalia and removal internal structures that are inappropriate for the social sex, suitablity final result of phenotype and psychosocial outcome due to the selected gender in patient. Surgery consists in cytocopy genito-plasty,

clitoroplasty to maximize the anatomical function to increase the sexual function.[11] In our case, patient had been done for reconstruction surgery (penectomy and clitoplasty) from ambiguous genitalia into female external genitalia.

SUMMARY

We reported a case of classic simple virilizing congenital adrenal hyperplasia in three years old girl whom had done for reconstrucion surgery (penectomy and clitoplasty). The patient has been treated with corticosteroid for stress therapy before the surgery and continued with maintanance dose. The patient was treated by a team which consists of endocrinologist pediatric, pediatric urologic surgeon, plastic surgeon, a psychologist.The prognosis of this case was good.

REFERENCE

1. Pang SY, Wallace MA, Hofman L. Worldwide experience in newborn screening for classical congenital adrenal hyperplasia dua to 21-hydroxylase deficiency. Pediatrics. 1998;81:866-74.
2. Aman B Pulungan, Charles Darwin Siregar, Aditiawati, Erwin P. Soenggoro, Endang Triningsih, I Wayan Bikin Suryawan, et al. Korteks adrenal dan gangguannya. In: Jose RL Batubara, Bambang Tridjaja AAP, Aman B. Pulungan, editors. Buku ajar endrokrinologi anak. 1st edition. Jakarta : Badan Penerbit IDAI; 2010. p. 251-96.
3. Nikarn S, Lin-Su K, New MI. Steroid 21 Hydroxylase Deficiency Congenital Adrenal Hyperplasia. Endocrinol Metab Clin N Am. 2009;38:699-718.
4. Ganong W. The central nervous system and the synthesis and release of adrenocorticotrophic hormone. In: Nalbandov A, editor. Advances in Neuroendocrinology. 2nd edition. Urbana : University of Illinois Press; 1993. p. 92.
5. White PC, Spesier PW. Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency. Endocrine Reviews. 2000;21(3):S245-91.
6. Goto M, Piper Hanley K, Marcos J. In humans, early cortisol biosynthesis provides a mechanism to safeguard female sexual development. J Clin Invest. 2006;116:953-60.
7. Charmandari E, Hindmarsh PC, Johnston A, Brook CG. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency : alterations in cortisol pharmacokinetics at puberty. J. Clin. Endocrinol. Metab. 2001;86(6):S2701-8.
8. Honour SM, Hindmarsh PC. Management of altered hydrocortisone pharmacokinetics in a boy with congenital adrenal hyperplasia using a continuous subcutaneous hydrocortisone influsion. J. Clin. Endocrinol. Metab. 2009:94(9): S3477-80.
9. Falhammar H, Thoren M. An 88-year-old woman diagnosed with adrenal tumor and congenital adrenal hyperplasia: connection or coincidence? J. Endocrinol. Invest. 2005;28(5):S449-53.
10. Dreger A, Feder EK, Mattis AT. Prenatal Dexamethasone for Congenital Adrenal Hyperplasia. Bioethical Inquiry. 2012;9:277-94.
11. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency : an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 2010:95(9):S4133-60.