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SIMPLE VIRILIZING CONGENITAL ADRENAL HYPERPLASIA: Presentation in a Female Child with Genital Ambiguity undergoing Genitoplasty (A Case Report)

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Objective: our objective was to display the presentation of simple virilizing Congenital Adrenal Hyperplasia (CAH) with genital ambiguity and severe virilization of the external genitalia, influencing growth, height and weight, bone maturation, quality of life and hence undergoing genitoplasty. Surgical treatment was aimed to obtain a more natural psychological and sexual development and the type of surgical repair performed was tailored based on individual patient's anatomy findings. **Case**: we report a case of a 3-year old female with simple virilizing CAH, diagnosed due to genital ambiguity, severe virilization, clitoromegaly, external genital pigmentation, precocious pubic hair, previously was under treatment with glucocorticoid replacement therapy for 2 years since newborn and neglected due to discontinuing the hormonal treatment for one year duration, underwent several clinical studies including chromosomal study for sex determining, pelvic ultrasonography for internal anatomical details and bone age study for skeletal maturation, given stress dose steroids pre-operatively and followed by genital reconstructive surgery (genitoplasty). A clitorectomy and labioplasty approach were performed. At time of surgery cystoscopy was carried out prior to the surgical repair. **Results**: Management of virilizing CAH child with ambiguous genitalia demands multidisciplinary and interdisciplinary approach. The team's major challenge is to use the feasible means to make the least bad choice in order to select a gender able to match the individual identity, social identity, and behavioral identity. Surgical option should be tailored, one stage surgery, at early age and performed according to the individual anatomy findings.

Key words: congenital adrenal hyperplasia, simple virilizing, genital ambiguity, genitoplasty.

INTRODUCTION

Disorders of sex development (DSD) encompasses three main groups of patients: (1) the virilised 46, XX DSD essentially represented by congenital adrenal hyperplasia (CAH); (2) the undervirilised 46, XY DSD essentially represented by hypospadias; and (3) the chromosomic jigsaws essentially represented by mixed gonadal dysgenesis.[1] The most frequent presentation of DSD in the newborn period or during childhood or newly presenting adolescent is genital ambiguity and the management of this abnormal genitalia can be a difficult challenge for health-care professionals and requires holistic multidisciplinary and interdisciplinary approach as well.[2]

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive disorders resulting from deficiency of one of the five enzymes required for synthesis of cortisol in the adrenal cortex.

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Approximately 90-95% of CAH cases are caused by steroid 21-hydroxylase deficiency (21-OHD, known in biochemistry term as *CYP21* or *CYP21A2* and *P450c21*) and this genetic endocrinologic disorder accounts the most frequent form of the disease.[3] The clinical spectrum of 21-hydroxylase deficiency has quite broad forms, ranging from the most severe to mild one. Accordingly, the three clinical phenotypes have been described: classic salt-wasting, classic simple virilizing and non classic.

Virilizing CAH is known as the most common etiology of genital ambiguity. The severe classic form occurs one in 16,000 births worldwide.[4] Females affected with this severe, classic 21-hydroxylase deficiency are exposed to excess or high systemic level of adrenal androgens prenatally (starts about the seventh week of gestation) and are born with virilized external genitalia and thus such girls have ambiguous genitalia: a large clitoris, rugated and partially fused labia majora and a common urogenital sinus in place of separate urethra and vagina.

We report a case of a 3-year old female with simple virilizing CAH. Our objective was to

display the presentation of simple virilizing Congenital Adrenal Hyperplasia (CAH) with genital ambiguity and severe virilization of the external genitalia, influencing growth, height and weight, bone maturation, quality of life and hence undergoing genitoplasty. The goals of surgery are: (1) genital appearance compatible with gender; (2) unobstructed urinary emptying without incontinence or infections; and (3) good adult sexual and reproductive function.

CASE REPORT

The patient was born of a healthy Balinese couple and she was a long awaited child from the second pregnancy of the mother. This second pregnancy was obtained after 15 years of effort since the last pregnancy had been terminated at one month gestational age. The mother had never been treated with any drugs during pregnancy or encountered hormonal exposure in utero and she had no signs of androgen excess such as hirsutism, alopecia or clitoral hypertrophy (maternal virilization). There was no family history of infertility, ambiguous genitalia or unexplained neonatal death. The patient had not developed conditions such as vomiting, impaired consciousness and severe dehydration at newborn. Laboratory findings revealed no hyponatremia (Natrium: 140 mmol/L), hyperkalemia (Kalium: 4, 1 mmol/L), and hypoglycemia (Blood sugar: 74 g/dL). The classic CAH due to 21-OH-deficiency was strongly had been suspected by reason of her clinical examination and symptoms. Serum hormones study confirmed the diagnosis. The result of serum 17-OH progesterone pediatric was over 1200 ng/dL (high), morning cortisol serum was 3, 34 µg/dL (low) and evening cortisol serum was 6, 48 µg/dL (normal). Hormonal replacement therapy using methyl prednisolone was given furthermore as the main treatment for two years. Due to seeking alternative medicine the patient discontinued the treatment for one year duration. As a consequence rapidly enlargement of the phallus has been occurred and brought the parents to seek an advanced treatment for the patient due to psychological distress.

A thorough physical examination showed symmetrical genitalia with phallus is more than clitoral size/severe virilization (Prader grade IV, 4 cm in length), external genital pigmentation, no palpable gonad within the labioscrotal folds, precocious pubic hair (Tanner scale II), clitoromegaly and ambiguous genitalia.

The patient previously has not been evaluated with a chromosomal analysis study and therefore gender assignment has not been made. The genetic study performed later on confirmed the karyotype was female of 46, XX. The karyotype in combination with an increased 17-hydroxy progesteron (17OHP) confirmed the likely diagnosis of a 46, XX, DSD with androgen excess caused by Congenital Adrenal Hyperplasia/CAH (Figure 1). The pelvic ultrasound is normal and the presentation of uterine was identified. Urogenitography study had not been performed and Intravenous Pyelography (IVP) as a substitute disclosed normal anatomy and kidney function. Her height was 100 cm, weight was 15.5 kg, Body Mass Index (BMI) for age is 15.5 kg/m^2 (normal).

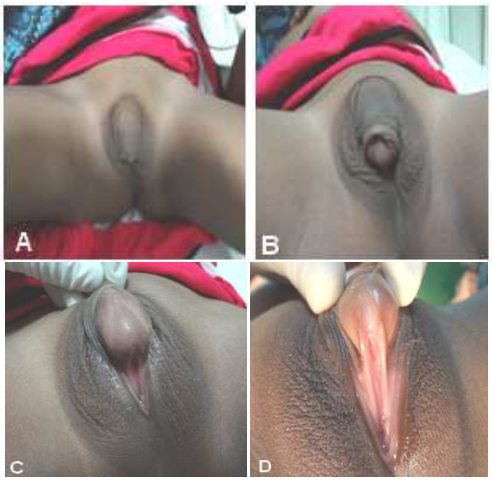

Figure 1
Simple Virilizing Congenital Adrenal Hyperplasia/CAH Patient

A. External genitalia appearance. Precocious pubic hair with external genitalia pigmentation shown.
B. Severe phallus enlargement (Virilization Prader grade IV, 4 cm in length). Labioscrotal fold exists without palpable gonad.
C. Clitoromegaly.
D. Orificium Urethra Externa (OUE) was identified. Hipoplasia vagina was found upon gynecologic consultation.

Bone age study affirmed the patient's bone development is appropriate with a girl aged 6 years 10 months old (Figure 2).

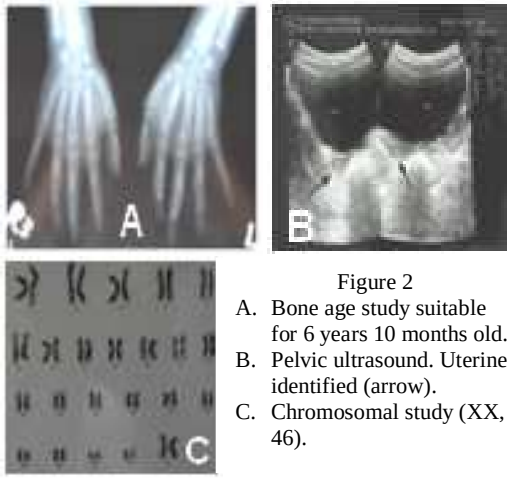

Figure 2

A. Bone age study suitable for 6 years 10 months old.
B. Pelvic ultrasound. Uterine identified (arrow).
C. Chromosomal study (XX, 46).

The parents were informed of the diagnosis and rearing a female sex was agreed and gave informed consent. This operation was approved by The Regional Ethical Review Board in Indonesia by the Committee Ethics of Sanglah General Hospital/Faculty of Medicine Udayana University, Bali-Indonesia.

The patient in such a way starts continuing the hormonal replacement treatment with methyl prednisolone and stress dose steroids preoperatively was given because the enzymatic defect blunts the physiologic adrenal responses. A genital reconstructive surgery (clitorectomy and labioplasty) was performed due to severe virilization, inadequate medical therapy and psychological distress. Cystoscopy was performed at the time of surgery prior to genitoplasty in order to confirm the anatomical relationship of the vagina to the urethra and external urethral sphincter (Figure 3 and 4).

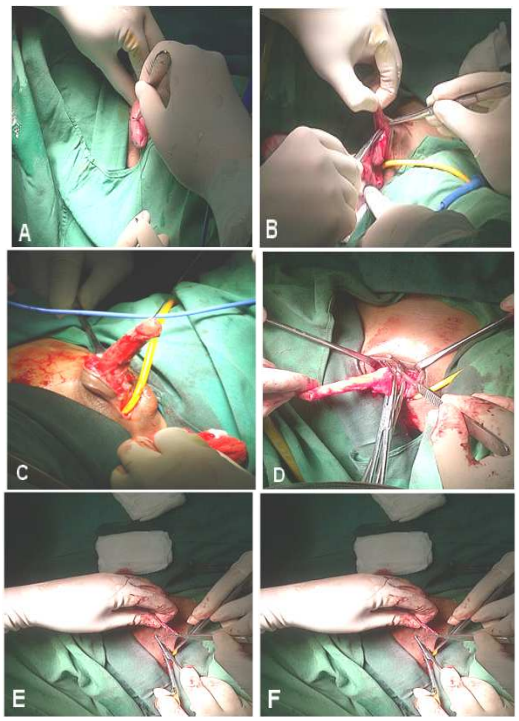

Figure 3
A. Cystoscopy was performed prior to surgery. Circumcising incision & mobilizing skin of clitoral shaft back to the pubis at the level of Buck's fascia.
B. Dividing dorsal aspect of preputial skin to create Byar's flap.
C. Corporal bodies of the virilized phallus.
D. Cliterectomy was performed (1).
E. Cliterectomy approach (2).
F. Labioplasty approach.

After surgery the patient will be followed periodically for a routine control of serum hormones study in order to adjust the medication dosage and vaginoplasty after puberty has been scheduled. A psychological support was encouraged to adjust several problems pre and post operative.

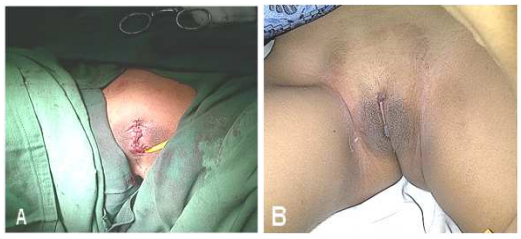

Figure 4
A. Post surgical appearance.
B. Post operative (Follow up day 7).

DISCUSSION

Congenital adrenal hyperplasia (CAH) is an inherited enzymatic defect of steroid synthesis that manifests with varying degrees of physical stigmata including virilizing of female patients. The females born with this disease disclose varying degrees of masculinization of their genitalia. The degree of stigmata diverges according to the underlying enzyme deficit altering cortisol in the adrenal gland and the most commonly encountered defect is of the 21-hydroxylase enzyme.[5] Approximately 50% of patients with CAH due to *CYP21A* mutations or deletions have salt wasting because of inadequate aldosterone synthesis. Mutation or partial deletion that affect *CYP21A* are common, with estimated frequencies as high as 1 in 3 individuals in selected population to 1 in 7 individuals in New York, United States. The estimated prevalence is 1 case per 60 individuals in the general population whilst in selected population (e.g. the Yupik Alaska) the prevalence is as high as 1 case in 400 populations.[6] Internationally, CAH caused by 21-OHD is found in all populations and occurs among people of all races.

Patients with simple virilizing 21-hydroxylase deficiency are usually diagnosed in female patients shortly after birth owing to genital ambiguity. Mild forms 21-hydroxylase deficiency in females are identified later in childhood because of precocious pubic hair, partial or complete fusion of the labioscrotal folds, phallus enlargement to clitoromegaly and often accompanied by accelerated growth and skeletal maturation due to excess and post natal exposure to adrenal androgens either are not untreated or are inadequately treated. Long term exposure to high levels of sex hormones leads to premature epiphyseal fusion (predominantly an effect of extragonadal aromatization of androgens to estrogens). Pubic and axillary hair may develop early. Clitoral growth may continue in girls. Long term exposure to androgens may also activate the hypothalamic-pituitary-gonadal axis, causing

centrally mediated precocious puberty. In our case, lack of patient's compliance in hormonal treatment for one year accounted for the presentation of severe virilization, precocious development of pubic hair, and accelerated growth and advanced skeletal maturation due to high systemic long term of androgens exposure. Short stature is a frequent complication of virilizing CAH. In general, patients have final heights 1-2 standard deviations below their estimated genetic potential.[7] Early central puberty is often observed in children with advanced skeletal maturation and contribute to the limitation of growth. Some patients develop precocious, perhaps secondary to the advanced growth and skeletal maturation. Short stature in adulthood is frequently the outcome in virilizing forms of adrenal hyperplasia because of the effect of uncontrolled adrenal androgens on skeletal maturation or the effects of excess glucocorticoid administration on growth. This may be treated with GnRH analogue therapy. Growth hormone in combination with GnRH agonist may improve adult height.

Ultrasonography by an experienced sonographer is often employed to visualize the presence of female reproductive organs. It is important to establish the exact location of the vagina in relation to the bladder. Particular attention must be made to delineate the size of the vagina and most importantly the level of the confluence of the vagina with the USG.[8] This information is invaluable in preoperative planning as well as for counseling parents regarding the extent of surgery required for vaginoplasty. Urogenitography may be an advantage to assess urethra, the presence of vagina, its relationship to the urethra, the level of the external sphincter, cervical impression and any fistulas or complex tracts. The classic classification of Prader relates the degree of external virilization to the level of confluence between vagina and urethra[9] is basically not essential and correct.[1] There is no relation between the external and internal aspects of the anomaly. Other classifications[10] have been published to provide a more accurate status of the genital anatomy.

All children undergoing genitoplasty of any forms should undergo preoperative antimicrobial prophylaxis. Additionally, some patients with 21-OHD may need stress dose steroids preoperatively if the enzymatic defect blunts the physiologic adrenal response to surgical stress. In conjunction with surgery, children with DSD should undergo counseling to help both the parents and child cope with physical and developmental abnormalities caused by the syndrome.

Females who present with adrenal hyperplasia have a wide range of anatomic findings. The mildest variety of the syndrome is the presence of a low vagina. The severe end of the spectrum is the virilized child with a high vagina entering into a masculine appearing urethra at the area of a false veromontanum (colliculus seminalis). Here the vagina enters proximally to the external urethra sphincter. The surgical approaches to the low and high vaginal entry are different. Cystoscopy also expedites catheterization of the vaginal introitus which makes intraoperative identification of pertinent anatomy easier. In our case, veromontanum appearance endoscopically was absence and urethtra orifice was found ventrally to introitus vagina.

Surgical management of patient with ambiguous genitalia has evolved continuously since Hendron and Crawford described the management of adrogenital syndrome in 1969. Several types of repair exist. The type of surgical repair performed must be tailored according to each individual patient's anatomy.[11] The first important issue is the timing of the reconstruction. This has been a controversial area in the past, but presently the standard of care is to perform reconstructive surgery at early age rather than delaying until adolescence. Reconstruction is generally commenced between the ages of 3 and 6 months old. The two main advantages of early reconstruction surgery are: (1) the availability of genital tissues and their quality is much better during the first 6 months of life. The urethral tissue is an essential material to refashion the low genital tract. (2) more psychological impact of late surgery is more profound than it is during the neonatal period for the child and parents. An early one stage repair is recommended[12, 13] and becomes standard of care because female patients are able to undergo a more natural psychological and sexual development when they have a normal appearing vagina. The major features of reconstructive genitoplasty are cliteroplasty, labioscrotal reduction and vaginal exteriorization (vaginoplasty).

Clitorectomy was recommended procedure in the past. One of the advantages is the complete removal of the corpora cavernous, which cannot grow again later in life if the patient less compliant to the hormonal treatment, which is a common situation during adolescence. It was initially advocated because those virilized females with clitorises left intact had erectile tissue that become painfully enlarged upon sexual arousal. In our case, clitorectomy was performed by reason of those advantages and the severity of clitoral hypertrophy (virilization). However, clitorectomy is no longer performed nowadays because it interferes with female sexual learning, appearance and development. Instead, a reduction clitoroplasty is performed in favor with the following goals in mind. The bodies of the clitoris and neurovascular bundles are preserved, while the glans is left intact. Approach to the clitoroplasty leaves the patient with intact clitoral sensation, painless sexual

arousal, a viable and sensate glans clitoris and appropriate erectile function during sexual arousal.[1, 5, 11] Nevertheless, the outcome of new technical evaluations needs to be evaluated in a few years time. The main question that is still raising controversies, besides when is the perfect time of surgery reconstruction, is above which size the genital tubercle should be reduced.

CONCLUSSION

Management of virilizing CAH child with ambiguous genitalia demands multidisciplinary team approach. Various specialties such as pediatric endocrinologist, urologist, psychologist, gynecologist should work as a teamwork to achieve a normal physiologic, emotional and sexual development.

The team major challenge is to use the tools available to make the least bad choice in order to select a gender able to match the individual identity, social identity, and behavioral identity. Patients well being can be achieved by team work, sustained follow-up and patient's compliance. Surgical option, performed by experienced surgeon or pediatric urologist, should be tailored, single stage surgery, at early age and executed according to the individual anatomy findings.

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