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Disorder of Sex Development, Mosaic Genetic Disorder 45X, 46XY: A Case Report

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ABSTRACT

Background. Disorder of sex development (DSD) is a congenital disorder associated with interference in chromosomes, gonads, or sexes anatomically. Individuals affected with DSD can be recognized since birth due to external genital ambiguity. Sexual chromosome DSD occurred because of sexual chromosome numeric or structural disorder. Mosaic karyotype 45X/46XY is among the rare sexual chromosome DSD with an incidence of less than 1:15,000 live births. DSD individuals are susceptible to stigmatization. This can cause stress, negative emotion, and social isolation. Therefore, DSD individual management should be done as optimal as possible.
Case Presentation: Twelve years old girl complained a bump arose from the anterior side of her genital resembles male genital since 4 years prior to admission without micturition and defecation complaints. The patient has not experienced menarche. On external genital examination, we found the normal female external genital such as mons pubis, pubic hair, labia majora, labia minora, hymen, perineum, but without clitoris which in this case it is replaced by a glans of the penis, arising from anterior commissure of labia majora area, with a urethral estuary. Before the management is done, the patient underwent multidiscipline consultations and further examinations. Subsequently, it was approved that the joint conference formation consisting of obstetric and gynecology, urologist, and pediatric endocrinologist to determine the optimal management for the patient.
Conclusion: In this case, the diagnosis was made with history taking, clinical examination, and supporting investigation such as ultrasound imaging and could be followed by biochemistry test, voiding cystourethrography, or genitogram to determine next management. Counseling should be done in detail towards the family to know what action is best for the patient. A multidiscipline team was required to get the optimum result either from a medical, ethical, or religious point of view. Surgery, in this case, was considered followed by long-term therapy afterwards.

1. Introduction

Disorder of Sex Development (DSD) is a congenital disorder associated with interference in chromosomes, gonads, or sexes anatomically.[1] Individual affected with DSD can be recognized since birth due to external genital ambiguity.[2] Sexual chromosome DSD occurred because of sexual chromosome numeric or structural disorder. Mosaic karyotype 45X/46XY is among the rare sexual chromosome DSD with an incidence of less than 1:15,000 live births.[3]

Individuals with DSD are susceptible to stigmatization. This can cause stress, negative emotion, and social isolation. Abnormal physical appearance could be harmful to psychosocial welfare. Therefore, DSD individual management should be done as optimal as possible.

2. Case Presentation

Twelve years old girl complained a bump arose from the anterior side of her genital resembles male genital

since 4 years prior to admission without micturition and defecation complaints. The patient has not experienced menarche. Secondary sex characteristics that had appeared were mustache hair and pubic hair, but no sign of the other characteristics such as voice change, armpit hair, and breast development. Her height was similar to her friends in the same age.

The patient was transferred to Dr. Mohammad Hoesin General Hospital Palembang by an obstetric-gynecologist of AR Bunda Hospital Lubuk Linggau with a diagnosis of a Disorder of Sex Development. Genetic analysis result was included with result showed [19EI-PB0593]: Mosaicism 45, X [16] / 46, XY [24].

Vital signs were in the normal range where blood pressure was 120/80 mmHg, heart rate of 80 times per minute, respiratory rate of 20 times per minute, and body temperature was 36,5^{o}C. On external genital examination, we found the normal female external genital such as mons pubis, pubic hair, labia majora, labia minora, hymen, perineum, but without clitoris which in this case it is replaced by a glans of the penis, arising from the anterior commissure of labia majora area, with a urethral estuary. Testicles, masses, or tenderness were not found. Due to the patient was not married yet the examination using a speculum and vaginal examination were not done.

In addition, laboratory findings showed increased testosterone level (86.50 ng/dL) and decreased estradiol level (<10 pg/mL), while other hormones level were in normal value, those were LH (16.28 mlU/L), FSH (75.47 mlU/L), Free T3 (3.31 pg/mL), and TSH (1.7365 µIU/mL). The blood test result was also in normal value which was hemoglobin 14 g/dL, leukocyte 10.66x10^{3}/mm^{3}, platelet 350,000/µL, and hematocrit 41%. Ultrasound showed uterine hypoplasia (2.64x1.48 cm) with both ovariums not visible. Lastly, genetic analysis test result was Mosaicism 45, X [16] / 46, XY [24].

Before the management is done, the patient underwent multidiscipline consultations and further examinations. The pediatric endocrinologist suggested further workup with genital ultrasound that showed infantile uterus with right ovarium was not visible and tiny left ovarium (volume of 0.49 mm^{3}). Besides, bone age imaging results showed average girls. And BNO IVP was also done but overall showed normal image except an anatomical variation of left kidney with duplex collecting system. The psychiatrist suggested additional therapy of family and individual psychotherapies. Subsequently, it was approved that the joint conference formation consisting of Obsgyn, urologist, and pediatric endocrinologist to determine the optimal management for the patient.

3. Discussion

Definition and etiology

Disorders of sex development (DSD) are defined as a congenital disorder associated with interference in chromosomes, gonads, or sexes anatomically.[1] Individual affected with DSD can be recognized since birth due to external genital ambiguity. Signs and symptoms could appear as virilization, not experiencing or delayed puberty or infertility. Sexual chromosome DSD occurred because of sexual chromosome numeric or structural disorder.[2] Mosaic karyotype 45X/46XY is among the rare sexual chromosome DSD with an incidence less than 1:15,000 live births.[3] This DSD has some phenotypes such as female with Turner syndrome, newborn with genital ambiguus commonly called mixed gonadal dysgenesis (MGD), and normal male development. MDG is the most common phenotype.[4, 5] Gonadal dysgenesis (ovarium agenesis, gonad displasia) is a clinical syndrome in which an individual has no secondary sex characteristic at puberty.[6]

The consensus of Lawson Wilkins Pediatric Endocrine Society (LWPES) and European Society for Pediatric Endocrinology (ESPE) classified DSD to: 1) Sexual chromosome DSD (45X Turner and the variants, 47XXY Klinefelter and the variants, 45X/46XY mixed gonadal dysgenesis (MGD) and chromosomal ovotesticular DSD (mosaic or chimeric type 46XX/46XY); 2) DSD 46,XY (testicular development disorder or androgen synthesis/action disorder); and 3) DSD 46XX (ovarian development disorder or fetal androgen excess).[1] In mosaic 45X/46XY individual, specific location in Y chromosome (gonadoblastoma locus) increased risk of malignant development of gonad cells.[2] The malignancy prevalence is 15-20%. Tumor development occurred

more commonly in the second decade of life. Malignancy should be suspected in 45X/46XY individuals who experiencing precocious puberty and breast development.[7]

Fetal chromosomes determine genotype sex. They modify primordial mesodermal cells through signaling pathways and hormones, resulting in cell differentiation to be phenotype sex. SRY *(sex-determining region Y)* gene played an important role in the sexual differentiation process. The embryonic gonad of both sexes could not be differentiated until the sixth week of pregnancy. Testicles will be formed in 46XY chromosome individuals by SRY gene effect. Testicles could be identified morphologically first at the seventh to eighth week. Sertoli cells formed around tubules and generate Müllerian inhibiting factor (MIF), a hormone that causes Müllerian duct regression. Leydig cells produce androgen and testosterone-inducing Wolff duct to differentiate to become epididymis, vas deferens, seminal vesicles, and ejaculatory ducts. An individual without Y chromosome, gonad develops into an ovarium. Mullerian duct transformed into the uterine and uterine tube, while Wolff duct runs into regression. In the case of 45X chromosome individual, lack of X chromosome resulting the development of streak gonad because the second X chromosome is essential for ovarium development.[8] Mosaicism is the existence of two or more lineage chromosomes in the same individual. In the case of mosaic 45X/46XY, there is a lineage of monosomi X (45X) and male chromosome (46XY).[7, 9]

Steroid biosynthesis disorder due to autosomal recessive adrenal enzyme deficiency is resulting in a lack of cortisol and aldosterone production. Excess of compensatory androgen occurred after increased adrenocorticotropic hormone production in hypophysis that causes virilization. Excessive androgen exposure is associated with clitoromegaly and labioscortal folds fusion.[10]

Diagnosis

Diagnosis of DSD tends to be difficult because it is required a complex investigation.[1] First approach would be started with history taking including familial and prenatal history. Familial history is focused on: ambiguity, hirsutism, precocious puberty, amenorrhea, and infertility. Exogenous hormones consumption and oral contraception by the mother during pregnancy should be confirmed.[1]

Physical examination should be focused on genital anatomy and look for dismorphic characteristics or developmental anomaly.[13] Inguinal and scrotum or labial examination should also be done to determine gonad existence, location, size, and texture if palpable. Phallus size is measured with width and length. Individuals with phallus length less than 2.5 cm are usually considered a female. Rectal examination can be done to confirm uterine and cervix existence.[1] External genital examination to ensure whether gonad is palpable or not and virilization grade or Prader staging. Prader stage I-V shows increased virilization of female phenotype with mild clitoromegaly (stage I) to male phenotype with glandular hypospadias (stage V).[12]

Physical examination findings criteria suggestive of DSD including 1) genital ambiguity (i.e cloaca exstrophy); 2) female genital with clitoris enlargement and posterior labial fusion; 3) male genital with a bilateral undescended testicle, hypospadia, or micropenis; and 4) genital appearance and karyotype not appropriate.[1]

Subsequently, workups required to do are sexual chromosome confirmation with quantitative fluorescence polymerase chain reaction (QFPCR) and karyotype analysis. Karyotype analysis is a cytogenetic technique (G-banding) and is essential in the early classification of DSD to be one of three categories: sexual chromosome DSD, DSD46XX, or DSD46XY.[14] This test usually requires 2 to 3 days of waiting.[15] Genetic tests such as FISH and special molecular test for gene mutation screening (AR, SRY, SF1, WT1, CYP21, SOX9, DAX-1, 17β hydroxysteroid dehydrogenase, 5α-reductase-2) could be done if there is a clinical suspection.[13, 16] If sexual chromosome DSD identified, then it is not needed to do further genetical analysis.[14]

Other tests include AMH level, serum testosterone level, cortisol level, androstenedione, gonadotropine serum, and urinalysis. In certain conditions, additional hormone stimulation tests such as human chorionic

gonadotropin (hCG) are done to determine testicle function.[1]

Abdominopelvic ultrasound should be done to find Mullerian structure. A retrograde genitogram is done to evaluate urogenital sinus anatomy and to localize the position of the urethral and vaginal entrance to the sinus.[1] Voiding cystourethrography is also useful to evaluate urethral, vaginal, and cervical anatomy. Magnetic resonance imaging (MRI) could provide more detailed anatomical information due to the multiplanar. Computed tomography (CT) is the main modality to evaluate malignancy associated with DSD and evaluation of germinal cell tumor stage.[8]

Management

Decision-making in determining patient sex depends on several factors, such as sexual function, genital appearance, the possibility of hormonal therapy needs until adult, future fertility, and risk of malignancy associated with DSD. Options available to DSD individuals are surgery, hormonal therapy, and psychosocial therapy.[18] DSD individuals are susceptible to stigmatization. This can cause stress, negative emotion, and social isolation. Therefore, DSD individual management should be done as optimal as possible.[19, 20] Nowadays, ethical matter in DSD management is getting developed. Fifth World Congress on Family Law and Children's Rights (2009) had published guidelines associated with ethical considerations to manage DSD cases.[8]

Feminization surgery technique consists of clitoroplasty, labioplasty, and vaginoplasty. Surgery is intended to normalize menstrual flow, vaginal sexual intercourse, and cosmetic aspect. The recommendation said that genital surgery is not needed in a female with severely masculine external genital. Until now, there is no study that could determine the best time to do clitoroplasty or vaginoplasty. Besides, no long term study comparing the functional, cosmetic, and psychological outcome of early reconstructive surgery to a delayed (post-puberty) one.[13, 21] Patient with 45X/46XY who undergo surgery needs long term therapy of sexual steroid hormone to increase secondary sexual characteristics and to prevent osteoporosis.[7]

Hormonal therapy in DSD goals is to enhance overall physiological health, to normalize linear growth, avoid virilization, and to improve long-term outcomes. It also focused on sexual anatomical development.[10]

Hydrocortisone is given 10-15 mg/m^2/day in three divided doses. Fludrocortisone 0.1-0.3 mg/day is given as adjuvant if hyponatremia or plasma renin activity increased occurred continuously. Hydrocortisone is titrated to maintain a 17-hydroxyprogesterone level under 70 nmol/L. Fludrocortisone should also be titrated to maintain plasma renin activity in the normal range. If the patient pass puberty and longitudinal growth have stopped, glucocorticoid hormone therapy could be achieved through the administration of long-acting agents such as prednisolone or dexamethasone. These agents could decrease oligomenorrhea and enhance fertility. The patient's parents should be educated about the requirement of glucocorticoid dosage increment of two or threefold in a period of physiological stress such as fever.[10]

Puberty induction in DSD individuals is done to accelerate female secondary sexual characteristics development, puberty development and growth, to increase the bone mineral level, and to accelerate psychological development. Puberty average age in females is 11 years old. Delayed puberty is defined as puberty not occurring in 13 years old of age. In girls with DSD without secondary estrogen production due to disgenesis or gonadectomy, puberty induction can be started at 11 years old of age. Estrogen therapy usually began with a low dosage and increased gradually to adult dosage for one to two years. In females with uterus, add progesterone therapy after estrogen adult dosage is reached or earlier if menarche has occurred. Puberty induction using natural estrogen 17b-estradiol is used more than the synthetic or equine one. The 17b-estradiol can be given orally or transdermally. Oral 17b-estradiol dosage is 0.5 mg/day, increased with 6 month interval until an adult dosage of 2 mg/day, depending on clinical response (breast Tanner stage, bone age). Low dosage (1/6 or 1/4 adult dosage) is administered to avoid excessive bone maturation. Transdermal 17b-estradiol firstly applied 3.1-6.2 mcg per 24 hours, increased to adult dosage of 100 mcg per 24 hours. Estrogen therapy is

administered to maintain estradiol serum level at 300-400 pmol/L.[10] This therapy continues until the patient becomes an adult.

If the patient has a uterus, progesterone therapy should be added at estrogen adult dosage or menarche achieved because endometrium cancer risk associated with estrogen. Progesterone is also needed to induce the endometrial and menstrual cycle. Medroxyprogesterone acetate can be administered 10 mg per day for the last 7 days of the menstrual cycle. Adverse effects of estrogen therapy are liver disturbance, thromboembolic, and hypertension. These adverse effects are more common in synthetic estrogen than natural 17b-estradiol. Transdermal preparation does not pass through hepatic metabolism, so it is not hepatotoxic.[10]

DSD Girls who have functional gonad that produces androgen could have androgen biosynthesis disorder such as 17b-hydroxysteroid dehydrogenase deficiency or 5-alpha reductase deficiency, partial androgen insensitivity syndrome, or partial gonadal dysgenesis. Management, in this case, involves gonadectomy to get rid of testicle tissue and androgen production. Gonadotropin releaser hormone analog therapy to suppress gonadotropin and androgen production could also be given as goserelin acetate 10.8 mg subcutaneously, triptoreline acetate 11.25 mg intramuscularly, or leuroprolide acetate 30 mg intramuscularly every 12 weeks. Dosage interval could be adjusted further using gonadotropin level.[10]

Most mosaic 45X/46XY individuals have short stature. Even though the cause is not growth hormone (GH) deficiency, but GH therapy of 0.35 mg/kg/week is often administered. In short term, it showed significant results on the growth pattern.[22] However, the long-term outcome does not show a significant effect. The recent systematic review also showed a significantly increased risk of malignancy incidence in subjects administered with GH (2.74; 95% CI 1.18-54.1), so the long-term safety of GH therapy is still questioned.[2]

4. Conclusion

In this case, the diagnosis was made with history taking, clinical examination, and supporting investigation such as ultrasound imaging and could be followed by biochemistry test, voiding cystourethrography, or genitogram to determine next management. Counseling should be done in detail towards the family to know what action is best for the patient. A multidiscipline team was required to get the optimum result either in a medical, ethical, or religious point of view. Surgery, in this case, was considered followed by long-term therapy afterward.

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