MIXED GONADAL DYSGENESIS IN A SEVEN MONTH OLD BABY

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ABSTRACT

Mixed gonadal dysgenesis is a very rare case with genital ambiguity as a clinical manifestation. Diagnosis of this condition is emerging due to proper gender assignment and prompt treatment to achieve optimal physical and psychologic development. We reported a genital ambigous in a 7 month old baby, who was referred with enlargement of clitoris, an unpalpable testis, but with a high concentration testosteron serum level, an uterus from genitography, and a mosaic karyotype 45,X/46,XY. The working diagnosis of this baby is mixed gonadal dysgenesis. Patients is being evaluated by a multidisciplinary team and planned having laparoscopy. **[MEDICINA 2014;45:52-57]**

Keywords : *mixed gonadal dysgenesis, mosaic karyotype, ambiguous genitalia*

MIXED GONADAL DYSGENESIS PADA BAYI USIA 7 BULAN

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ABSTRAK

Mixed gonadal dysgenesis merupakan suatu penyakit yang jarang dijumpai dengan manifestasi klinis berupa ambigus genitalia. Penegakan diagnosis terhadap kondisi ini harus segera dilakukan untuk menentukan jenis kelamin, tata laksana tepat sedini mungkin untuk mencapai tumbuh kembang optimal. Kami melaporkan kasus ambigus genitalia pada bayi berusia 7 bulan yang datang dengan pembesaran klitoris, testis tidak teraba, kadar serum terstosteron tinggi, ditemukan uterus dari hasil genitografi dan kariotipe mosaik 45,X/46,XY. Pasien didiagnosis kerja dengan *mixed gonadal dysgenesis*. Saat ini pasien tetap dimonitoring oleh tim multidisiplin dan direncanakan menjalani laparoskopi. **[MEDICINA 2014;45:52-57]**

Kata kunci : *mixed gonadal dysgenesis, kariotipe mosaik, ambigus genitalia*

INTRODUCTION

The syndrome of mixed gonadal dysgenesis (MGD) is characterized by an unilateral testis, usually intra-abdominal, a streak gonad on the contralateral side, and persistent Mullerian structures. It has an extreme phenotypic variability postnatally that may extend from a Turner-like syndrome to a male phenotypic with a penile urethra.[1] Mixed gonadal dysgenesis is suggested as a second common cause of disorder of sex development (DSD) and the incidence is approximately 1 : 10,000 of newborn. Internally, 75% of patients with partial XY gonadal dysgenesis have an uterus because gonad produces enough *Mullerian Inhibiting Substancies* (MIS). In most cases of partial gonadal dysgenesis, a range of karyotypes is seen such as 45,XO/46,XY; 45,XY/XO; 46XX. One gonad is usually a streak, and another is likely to be a fairly well-developed testis in which Leydig cells can usually be identified. In the complete form of XY gonadal dysgenesis, both gonads are streaks.[2,3] The discrepancy between normal leydig cell function at puberty and an evidence of incomplete genital masculinization during fetal life may possibly be explained by a delayed and asynchronous fetal testicular development.[2,4,5]

Although patients with an unilateral gonadoblastoma and a contralateral streak gonad were included in the original description of the syndrome of MGD, most of those patients differ clinically and cytogenetically from patients with a testis and probably should be considered more akin to patients with a syndrome of pure gonadal dysgenesis, than to MGD.[2,5,6] Many problems in diagnosis of and therapy for this condition such as karyotyping in ambiguous genitalia is a widely recommended procedure, as it allows early diagnosis and early application of an appropriate therapy. Close follow-up for development of gonadal tumors is mandatory in all patients with 45,X/46,XY karyotype.[7] The primary aim

should be to achieve a diagnosis, sex assignment (if needed) and management plan as quickly as possible, but without rash decisions being made.[8,9] We report this seven months old baby who had the classical morphology features of mixed gonadal dysgenesis.

CASE ILLUSTRATION

R, a seven month old baby was referred to endocrinology outpatient Sanglah Hospital's clinic because of a slight enlargement of the clitoris. The parents worried about the size of the clitoris. They saw there was an enlargement of clitoris at their child, and it looks like a small penis. They realized this abnormality since 2 months ago and they had already discussed this problem to their family. They decided to see a pediatrician and then their child was referred to an endocrinology outpatient clinic to have some examinations. While waiting for the result of the examination, now, their child is already 7 months old, and the parents became more confused about the gender of their child.

She was born full term, normal, spontaneously, and birth weight was 2700 grams. She did not receive any prior medications for specific diseases. There were no history of having profuse vomiting after birth and hospitalized because of this condition, there were no hiperpigmentation on the patient as well. From the family history, the parents were 45 years old (father) and 42 years old (mother) at the child birth. The baby is the third child at this family, with two older sisters. The eldest one was 5 years old and the second one was 4 years old. Both of the sisters have normal growth and development. Neither of the parents or other family member have any signs and symptoms of sexual organ dysfunctions nor delayed puberty before. There were no prior history of receiving hormonal therapy and no medication throughout the course of gestation on the mother. The immunization history was complete according to the recommended immunization plan by Indonesian Pediatric Society.

Physical examination revealed an alert child, who looked active. Vital sign within normal limit. Chest examination, abdomen and extremities also within normal limit. Urogenitalia examination showed phalus measured 30 mm in length with a 5-mm base, without palpable testicular. Orifisium urethrae and introitus vaginae cannot be seen clearly (**Figure 1).**

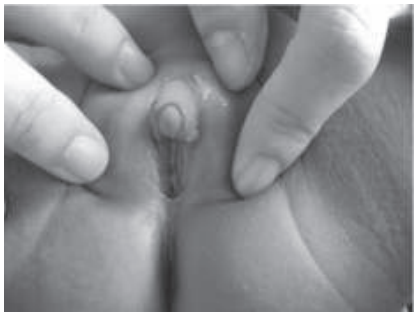

Figure 1. Appearance of the external genitalia.

Laboratory investigation revealed a normal cell blood count, electrolyte, and glucose. Testosterone concentration was 5 ng/mL (normal male at the age less than 1 years old, 12-21), and it decreased with age, progesterone 17-OH serum concentration was 12 ng/mL (range normal at the age less than 1 years old, 11-170 ng/mL). The chromosome analysis using G-banding showed a karyotype of 45,XO/46,XY as shown in **Figure 2.** Polymerase chain reaction (PCR) showed the presence of the sex-determining region Y. Using technique *Methapase Fluorescence in situ hybridization* (FISH) analysis with X chromosome-specific probes (control), there was three population cell (mosaic), including 138 cell (69%) without SRY gen, 59 cell (29.5%) with 1 SRY gen and 3 cell (1.5%) with 2 SRY gen as shown ini **Figure 3.**

Ultrasonography examination (genitography) was conducted to evaluate the genitalia. It revealed no abnormality of the urinary bladder (**Figure 4**). The contrast

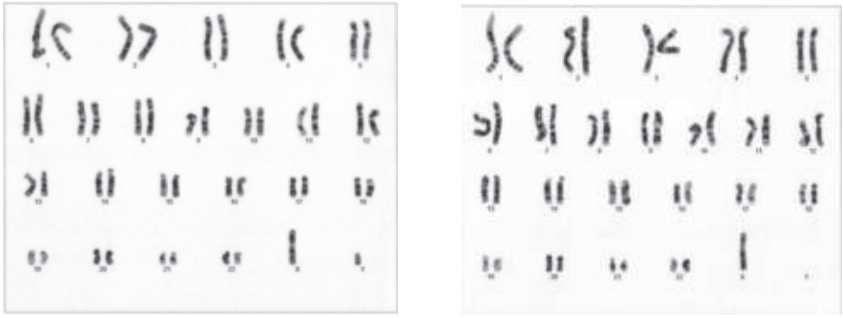

Figure 2. Chromosome analysis showed 45,XO/46,XY.

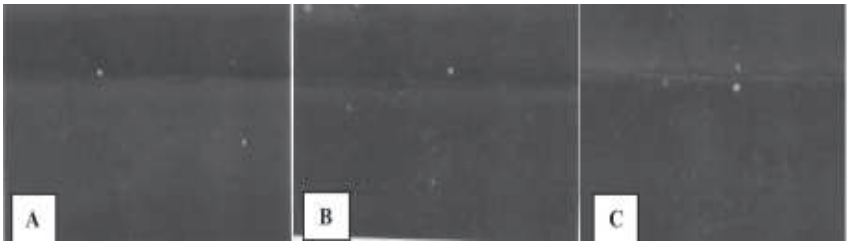

Figure 3. FISH analysis. (A) One green dot showed there was one X chromosome. The absence of red dot showed there were no SRY gene, (B) One green dot showed there was one X chromosome. Two red dot showed there were two SRY gene, (C) Presence of one green dot showed there was one X chromosome. Presence of one red dot showed there was one SRY gene.

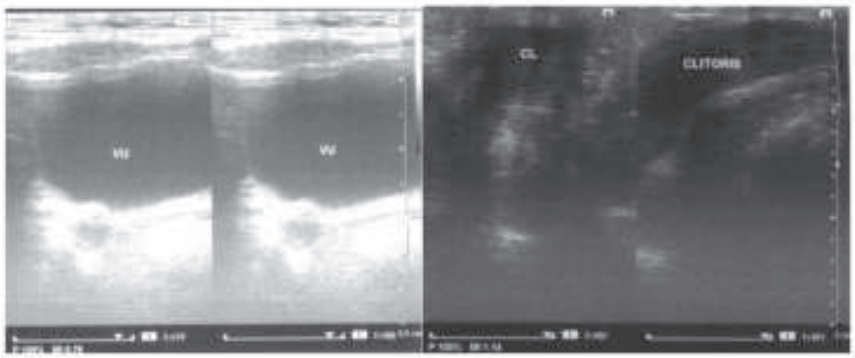

Figure 4. Ultrasonography examination. It revealed no abnormality of the urinary bladder.

study showed there was canal above the anal with 1 cm depth. The contrast injected into the canal made an oval-like shaped, sized 22.03 mm x 11.98 mm, plain edge, sharp on the inferior. There were no contrast extravasation to the cavum abdomen and also there was no contrast on vesica urinaria. It concluded that there was an uterus-like shaped (possibly a girl) (**Figure 5**).

Human chorionic gonadotropin (hCG) stimulation test using 1000 IU/day, revealed increasing level of testosterone hormone from 5 ng/mL to 302 ng/mL. Based on history taking, physical finding, laboratory and radiology examination, we suggested this patient suffered from ambiguous genitalia due to MGD with parsial androgen insensitivity syndromme (PAIS) and congenital adrenal hyperplasia (CAH) as a differential diagnosis. Laparoscopy is needed for gonadal evaluation and to diagnose MGD from biopsy specimen although we strongly suspected MGD in this case. Unfortunately in our region hospital, laparascopy procedure on child has not been conducted yet. Therefore, we recommend the patient to conduct laparascopy procedure in Cipto Mangunkusumo Hospital at Jakarta.

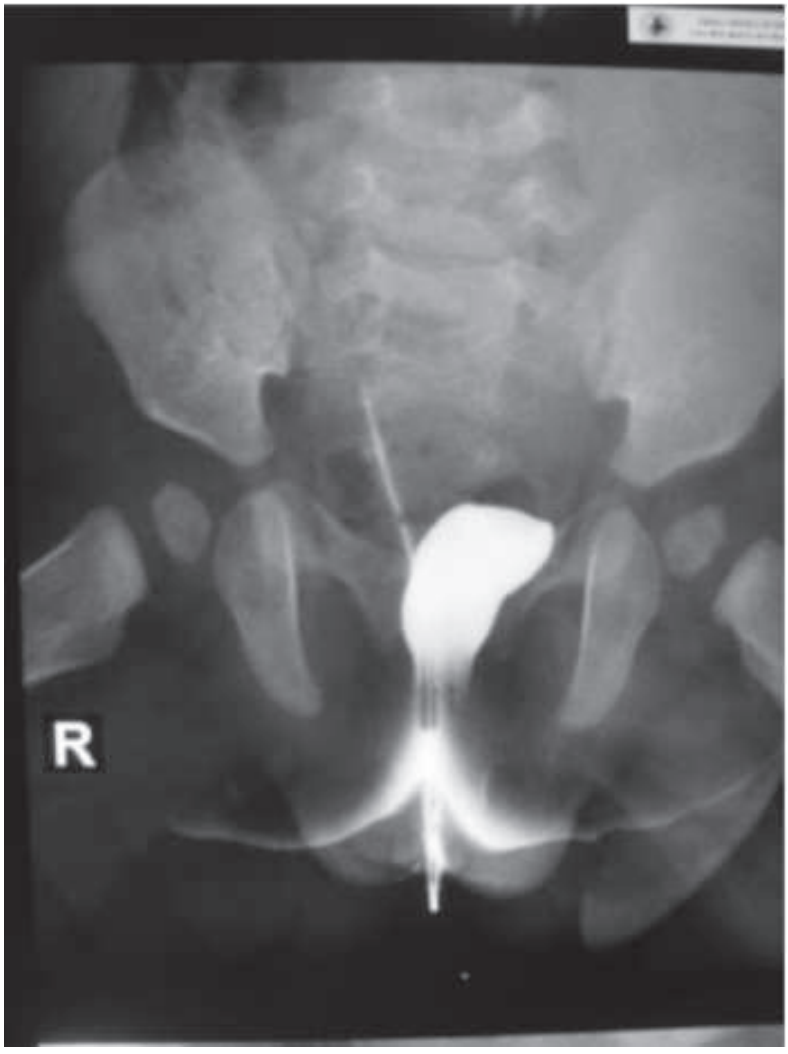

Figure 5. Contrast Study. It concluded that there was an uterus shaped-like.

DISCUSSION

Gonadal dysgenesis is defined on the basis of gonadal morphological features as an abnormal testis on one side and a streak gonad on the other side. The estimated incidence of clinically detectable ambiguous genitalia at birth in Germany is 2.2 per 10,000 births.[5,10]

The incomplete formation of the male external genitalia constitutes a defect in normal physical sex differentiation, which is related to the theory of hormonal dependence of male sexual differentiation. Gonadal dysgenesis is caused by abnormal testicular determination and differentiation. It could be expected that decreased androgen production results not only in phenotypic disturbances but also in changes of regulatory mechanisms in the central nervous system. The determinants of gender-related behavior patterns can be arbitrarily subdivided into neuroendocrine factors (principally the effects of testosterone on the brain) and sociocultural factors, which include sex of rearing, interactions with parents, siblings, and peers, and the culture

to which the individual is exposed. Excessive exposure to prenatal androgens may have a stronger impact on some components of psychosexual differentiation than on others (i.e., gender identity).[5,11] In our case the patient is seven month old baby, born term, risk factor for disturbance sexual differentiation such as hormone exposure during prenatal or perinatal factors and sociocultural factors were no found.

Mixed or partial gonadal dysgenesis (45,XO/46,XY or 46,XY) involves a streak gonad on one side and a testis, often dysgenetic, on the other side. Affected patients have ambiguous external genitalia and persistent Mullerian (female) duct structures. The genital phenotype is varied, ranging from a hypospadial penis and unilateral descended testis to female genitalia with varying degree of virilization. All these patients had female internal genitalia derived from Mullerian structures. MGD patients are shorter than normal.[5,8-10] In our case, on first addmission, the parents complain about clitoris enlargement of their daughter that realized since a month ago. Physical examination showed a 7 month old baby with 30 mm phalus length, unpalpable testis, and normal urine excretion.

Hormonal evaluations and imaging studies are sometimes useful to diagnose these patients, but they are not always definitive. An hCG stimulation test is required to assess Leydig cell function and testosterone production. Assessment of testosterone production after hCG stimulation could be useful in such patients, especially in the first year of life.[5,12] Testosterone response depend on the age of the patient.[5] The highest levels are observed during the first months of life. Testosterone levels are determined by radioimmunoassay (RIA) before and after stimulation. Imaging plays an important role in depicting the internal organs and urogenital anatomy in children with ambiguous genitalia. Ultrasonography is the primary modality for evaluation of the internal reproductive organs, whereas genitography and voiding cystourethrography are used for evaluation of urethral and vaginal tracts and fistulas. A gonad with the morphologic appearance of a testis or ovary on ultrasonography may prove to be a dysgenetic gonad at biopsy. At minimum, a rudimentary uterus or fallopian tube can be seen on the edge with the streak gonad. On the edge with the testis, local MIS diffusion prevents development of a fallopian tube. Fluorescence in situ hybridization as a molecular analysis is most useful and informative for detecting the SRY sequence and localizing the signal easily. Although several key factors are responsible for sexual differentiation and disorder of sex development (DSD), the presence of the SRY sequence often indicates the existence of a testicular component, even in a phenotypic girl, as well as the gene responsible for tumor formation in a dysgenetic gonad map close to the Y chromosome centromere, making the Y centromeric probe important for evaluation of marker chromosomes. In addition, Yq microdeletions may be associated with Y chromosomal instability leading to the formation of 45,XO cell lines; however, as a result, gonadal biopsy is sometimes necessary to establish the correct final diagnosis and subsequent treatment.

Laparoscopy provides an excellent view of the intraabdominal gonad and internal genitalia by magnification, maintaining a wide space, easy access to the pelvic cavity and adequate illumination, and is helpful for correct diagnosis.[5,8,13,14] In our patients, there were high testosterone serum level hCG stimulation test. It means there were gonadal function. Ultrasonography examination (genitography) showed there was a canal above the anal with 1 cm depth, oval shaped-like, sized 22.03 mm x 11.98 mm, concluded that there was an uterus-like shape. Polymerase chain reaction showed the presence of the sex-determining region Y (SRY) sequence. Using technique *Methapase Fluorescence in situ hybridization* (FISH) analysis with X chromosome-specific probes (control), there were three population cells (mosaic), including 138 cell (69%) without SRY gen, 59 cell (29.5%) with 1 SRY gen and 3 cell (1.5%) with 2 SRY gen. We planned to perform an initial laparoscopic approach for gonadal evaluation and diagnose MGD from biopsy specimens. Laparoscopy was not performed yet because laparoscopic procedure on baby has not been conducted yet in our region hospital and also prepare physical and physicological factor of the patient and parent. Finally, according to doctor recommendation, parents decided to bring their child to Cipto Mangunkusumo Hospital at Jakarta to perform laparoscopic procedure immediately.

Patients who raised as girls, streak gonads and any testicular tissue were excised and feminizing genitoplasty were performed in childhood. In addition, hormone replacement therapy was given at pubertal age. In all patients raised as boys, streak gonads and Mullerian structures were excised and the penis reconstructed. The procedure of penis reconstruction is complicated, consisting of multiple stages. It began in early childhood and, in some patients, was completed at late peripubertal age (from mullerian ducts removal to plastic surgery of the urethra), hence surgical removal of the gonad is recommended. Patients with a 45,XO/46,XY karyotype and normal testis biopsy could retain the testis if it is descended or can be placed in the scrotum. These children would then need a close follow-up of the testis by monthly self examinations for tumor

formation. Laparoscopic management is a good approach for patients with DSD, including MGD because it enables minimally invasive surgery for children and all necessary procedures, including evaluation, biopsy, and gonadectomy for diagnosis and treatment. [5,8,10,13] In our case, the parents want to raise the child as a boy. It is difficult to distinguish the sexual gender. However, we strongly identified the presence of a testicular component from the presence of SRY on the polymerase chain reaction and high testosterone serum level after hCG stimulation test. Now, we plan to evaluate the intraabdominal gonad and internal genitalia using laparoscopy to provide an excellent view. After we find testis intraabdominal, testis can be descended and placed in the scrotum, so it can reach their function normally. Unfortunately, laparoscopy procedure can not perform yet in our region. Therefore, we recommend to refer the patient to other hospitals which can perform this procedure. The next step if the parents still wants to raise their child as a boy, streak gonads and Mullerian structures were excised and the penis reconstructed. Although the child is now within normal length and weight, the child will require growth hormone in the future because consistent with previous reports, where MGD patients are shorter than normal. A dysgenetic gonad increases the risk of gonadoblastoma and seminoma; therefore, it should be removed.

Patients with a Y chromosome in the karyotype are at a higher risk than the general population to develop a tumor in the streak or dysgenetic gonad. Gonadoblastoma, a benign growth, is the most common tumor because of the 20% to 25% age-related risk for malignant transformation into a dysgerminoma.[10,15] This syndrome has generated considerable interest as a possible precursor to, marker of, or risk factor for germ-cell neoplasia or carcinoma in situ.[10] Sex assignment is usually difficult in patients with major ambiguous external genitalia. Careful evaluation and correct diagnosis are very important to prevent therapeutic errors and gonadoblastoma because 15%–20% of children with MGD develop a gonadal neoplasm within the 1st or 2nd decade of life. That is why one of the important management is streak gonads on patient with mixed gonadal dysgenesis should be removed.[6,8,10,15]

SUMMARY

We reported a 7 month old baby admitted with clitoris enlargement and unpalpable testis. There were high testosterone serum level after provocation test, an uterus shaped-like from genitography, and a mosaic karyotype 45,X/46,XY. History of hormone exposure during prenatal or perinatal and sociocultural factors as a risk factor of disturbance sexual differentiation were no found. The patient was diagnosed with MGD and refer to other hospital for laparoscopy.

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