THE ROLE OF UROLOGISTS IN MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

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ABSTRAK

Tujuan Penelitian: *Mengetahui gambaran kasus disorder of sex development (DSD), alur penanganan kasus serta peran ahli urologi dalam tatalaksana diagnosis dan terapeutik DSD di RSUPN Cipto Mangunkusumo (RSCM) Jakarta.* ***Bahan & Cara:*** *Kami melakukan penelitian deskriptif retrospektif terhadap data yang diperoleh dari rekam medis kasus yang ditangani oleh tim endokrinologi anak, urologi, dan kebidanan RSCM dalam periode Januari 2002 sampai dengan Desember 2009. Kriteria IICP 2006 digunakan sebagai klasifikasi kelompok DSD. Alur penanganan kasus dan peran ahli urologi dievaluasi.* ***Hasil Penelitian:*** *Terdapat 133 kasus DSD selama periode penelitian, kasus congenital adrenal hyperplasia (CAH) merupakan kasus tersering yang ditemukan diikuti kasus androgen insensitivity syndrome (AIS). Sebagian kasus didiagnosis saat usia bayi dan sebagiannya lagi saat usia pubertal. Telah dilakukan sejumlah upaya diagnostik meliputi analisa kariotipe, pemeriksaan laboratorium, ultrasonografi, genitografi, uretrosistoskopi-kolposkopi, laparaskopi diagnostik. Gender assignment dilakukan dengan melibatkan tim multidiplin. Jenis operasi yang telah dilakukan meliputi masculinizing surgery, feminizing surgery, dan gonadektomi.* ***Simpulan:*** *Gambaran kasus DSD di RSCM sebagian besar merupakan kasus CAH. Alur penatalaksanaan kasus DSD telah melibatkan tim multidisiplin. Upaya diagnostik yang menyeluruh penting dilakukan sebelum gender assignment dilakukan. Ahli urologi berperan penting dalam upaya diagnostik dan upaya terapeutik.*

Kata Kunci*: Disorder of sex development, upaya diagnostik, gender assignment, upaya terapeutik, ahli urologi.*

ABSTRACT

Objective: *To evaluate disorder of sex development (DSD) profile at Cipto Mangunkusumo Hospital (RSCM), the management profile, and the role of urologist on diagnostic and therapeutic management.* ***Material & method:*** *We retrospectively collected data from medical record of all DSD cases managed by pediatric endocrinologist, urologist, obstetric gynaecologist at RSCM from January 2002 up to December 2009. 2006 IICP criteria was used as classification. The management profile and the role of urologist were evaluated.* ***Results:*** *there were 133 DSD cases with the majority of cases was congenital adrenal hyperplasia (CAH) followed by androgen insensitivity syndrome (AIS). Most of the cases were diagnosed before one year old and other on pubertal period. Karyotyping, laboratory examination, ultrasonography, genitography, uretrocystoscopy, kolposcopy, diagnostic laparascopy were performed as diagnostic management. Gender assignment was performed by multidisciplinary team. Masculinizing surgery, feminizing surgery, and gonadectomy was done as therapeutic management.* ***Conclusion:*** *The majority case on RSCM's DSD profile was CAH. The management was performed by multidisciplinary team. Gender assignment decision should be based upon thorough diagnostic evaluation. The urologist has important role on diagnostic and therapeutic management.*

Keywords: *Disorder of sex development, diagnostic management, gender assignment, therapeutic management, urologist.*

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INTRODUCTION

Disorder of sex development (DSD) is a congenital abnormality characterized by the incompatibility between the sex chromosome, gonads, or the sex phenotype.[1] It is a rare abnormality with the estimated incidence of 1 in every 2.000 live births.[2] Others reported the incidence of 1 in every 4500 live births.[3] The abnormality can be diagnosed during infancy or during adulthood.

The classification of DSD is still varied along with the development of science and understanding about the disease. One of the classification proposed by The International Intersex Consensus Conference Participant (IICCP) in 2006 is as follows.

The main objective of the management of DSD is to establish a diagnosis, to make gender assignment when necessary, and to initiate therapy as soon as possible.[4] The DSD management encompasses diagnostic and therapeutic management. The diagnostic efforts include the physical examination, laboratory examination, chromosome analysis, diagnostic radiology and diagnostic laparoscopy. The therapeutic efforts include gender assignment, medication, surgery, and psychosexual therapy.[5] Some of the concerns of the objectives of DSD management are reproduction potentials, sexual potentials, minimally-invasive surgery, a gender appropriate physical appearance, a consistent gender identity, and a satisfying psychosocial sentiment.[1]

The management of DSD should be carried out by a multidisciplinary team working together in a tertiary institution. The team should include an endocrinologist, urologist, geneticist, gynecologist, and a psychiatrist.[4] This multidisciplinary team should always consists of a urologist. Usually, the urologist becomes the first line consultant, especially in an institution without a multidisciplinary team.[4]

The urologist plays a role in the diagnostic and therapeutic management. The diagnostic management conducted by urologists are anamnesis, physical examination including the one conducted under anesthesia, laboratory examination and

Table 1. DSD Classification proposed by IICCP 2006.

Sex Chromosome DSD	46 XY DSD	46 XX DSD
A. 45,X0 (turner syndrome and variants)	A. Disorder of gonadal development 1. Complete gonadal dysgenesis (swyer syndrome) 2. Partial gonadal dysgenesis 3. Gonadal regresion 4. Ovotesticular DSD	A. Disorder of gonadal development 1. Ovotesticular DSD 2. Testicular DSD (SRY+) 3. Gonadal dysgenesis
B. 47XXY (klinefelter syndrome and variants)	B. Disorder in androgen syntesis or action 1. Androgen biosyntesis defect (eg. 5 a reductase deficiency) 2. Defect in androgen action(eg. complete/partial androgen insensivity syndrome (CAIS/PAIS)) 3. LH reseptor defect(leydig cell hypoplasia/aplasia) 4. Disorder of AMH or AMH receptor (persistent mullerian duct syndrome)	B. Androgen excess 1. Fetal (Congenital adrenal hyperplasia (CAH)) 2. Fetoplacental (aromatase deficiency, POR) 3. Maternal (luteoma)
C. 45X/46XY (mixed gonadal dysgenesis, ovotesticular DSD) D. 46XX/46XY (chimeric, ovotesticular DSD)	C. Other (severe hipospadia, cloaka extrophy, aphalia)	C. Other (cloaka extrophy, vaginal agenesis)

chromosome analysis, imaging with ultrasonography, genitography, uretrocystoscopy and laparoscopy.[6] The therapeutic management which can be conducted by the urologists are masculinizing surgery, feminizing surgery, and gonadectomy.

OBJECTIVE

To evaluate the case profile of DSD in RSCM, the case management, and the role of urologist in the management of diagnosis and therapy of DSD in RSCM.

MATERIAL & METHOD

We conducted a retrospective descriptive study using the medical records data of the cases handled by the pediatric endocrinology, urology and obstetrics and gynecology team of RSUPN Dr. Cipto Mangunkusumo during the period of January 2002 to December 2009. The data collection included the type of DSD, the patients' age, sex of rearing (the type of rearing based on certain gender), diagnostic efforts, gender assignment (the gender of choice based on mutual consensus) and the type of therapeutic effort which will be conducted.

The DSD type is established from the findings in physical, laboratory and karyotype examination. Afterwards, the data will be classified based on the classification of 2006 IICP. The existing data is processed using SPSS v 17.0.

RESULTS

During the period of January 2002 to December 2009, the multidisciplinary team of RSUPN Cipto Mangunkusumo had managed 133 DSD cases. The number and percentage of each type of DSD cases and its classification according to the 2006 IICP can be seen in table 2.

The age of the patient at the time of the diagnosis is divided into four age groups, infant (1 year old), toddlers (1-5 years old), prepubertal (6-10 years old) and pubertal (> 11 years old), which can be observed in table 3, and sex of rearing can be seen in table 4.

Genitography, uretrocystoscopy-colposcopy, and diagnostic laparoscopy are carried out as diagnostic management. The genitography is performed by a radiology team, while the uretrocystoscopy-colposcopy and diagnostic laparoscopy is performed by the urologist team. The numbers of each diagnostic management can be seen in table 5.

Table 2. Frequency and percentage of each DSD type and its classification based on IICCP 2006*

DSD Type		Frequency	Percentage
Sex chromosome DSD	Turner syndrome	15	11,3
	MGD[1]	9	6,8
46 XY DSD	AIS[2]	18	13,5
	5 alpha reduktase deficiency	4	3,0
	Aphalia	1	0,8
	Gonadal dysgenesis	1	0,8
46 XX DSD	Ovotesticular	3	2,3
	CAH[3]	75	56,4
	Vaginal atresia	2	1,5
Not yet underwent full workup		5	3,8
Total		133	100

*not included severe hypospadia and cloaca extrophy cases
[1] Mixed gonadal dysgenesis
[2] Androgen insensitivity syndrome
[3] Congenital adrenal hyperplasia

Table 3. Distribution of age at diagnose and management of each DSD types.

		Age Classification				
		Infant (< 1 yrs)	Toddler (2-5 yrs	Prapubertal (6-10 yrs)	Pubertal (> 11 yrs)	Total
Sex chromosome DSD	Turner syndrome	0	0	1	14	15
	MGD[1]	2	4	1	2	9
46 XY DSD	AIS[2]	0	1	0	0	1
	5 alpha reduktase deficiency	0	0	1	3	4
	Aphalia	6	5	1	6	18
	Gonadal dysgenesis	1	0	0	0	1
46 XX DSD	Ovotesticular	1	1	0	1	3
	CAH[3]	50	15	7	3	75
	Vaginal atresia	0	0	0	2	2
Not yet underwent full workup		4	1	0	0	5
Total		64	27	11	31	133

[1] Mixed gonadal dysgenesis [2] Androgen insensitivity syndrome [3] Congenital adrenal hyperplasia

Table 4. Sex of rearing of each DSD types.

		Sexofrearing		Total
		Male	Female	
Type	Sex chromosome DSD	2	22	24
	46XYDSD	15	9	24
	46XXDSD	13	67	80
	Not yet underwent full workup	3	2	5
Total		33	100	133

Tabel 5. Additional examination.

	Genitography	Uretrocystoscopy-colposcopy	Diagnostic laparoscopy
Sex chromosome DSD	2	6	6
46XY DSD	-	-	1
46 XX DSD	1	6	2

During the diagnostic laparoscopy, the team evaluates the structure of internal genitalia which derives from the Mullerian structure and the structure of gonads. A biopsy can also be performed during this procedure. The biopsy results which was obtained in this study reported 3 cases showing testes and gonad streak, 1 case showing ovaries and testes, 1 case showing ovotestes, and 1 case showing prepubertal testes with gonadoblastoma testicular dysplasia.

After all of the data had been collected, the multidisciplinary team conducted a gender assignment by a conference involving the patients and the family. The results of gender assignment of the 133 DSD cases can be seen on table 6.

The therapeutic management of DSD includes medication and surgery. The types of surgery for these cases are masculinizing genitoplasty,

Table 6. Gender assignment.

		Gender Assignment			Total
		Male	Female	Not decided yet	
Type	Sex chromosome DSD	2	21	1	24
	46XYDSD	16	6	2	24
	46XXDSD	0	82	8	80
	Not yet underwent full workup	N/A	N/A	5	5
Total		18	109	16	133

Table 7. Therapeutic management of DSD.

Type DSD		Therapeutic Management	Freq
Sex chromosome DSD	Turner syndrome	Medication only	15
	Mixed gonadal dysgenesis	Clitoroplasty	2
		Clitorovaginoplasty + laparascopy gonadectomy	2
		Hypospadia repair	1
		None has been taken	4
46XY DSD	Gonadal dysgenesis	None has been taken	1
	AIS	Clitorovaginoplasty + laparascopy gonadectomy	1
		Hipospadia repair	2
		Hipospadia repair + orkidopecxy	1
		None has been taken	13
	Defisiensi 5-a reduktase	Hipospadia repair	3
		Plan to do hipospadia repair	1
	Aphalia	Phalloplasty	1
46 XX DSD	Ovotesticular	Clitorovaginoplasty + laparascopy gonadectomy	1
		None has been taken	2
	CAH	Clitoroplasty	15
		Clitorovaginoplasty	5
		Plan to do clitoroplasty/clitorovaginoplasty	7
		Medication only	48
	Vaginal atresia	Vaginoplasty	2

feminizing genitoplasty, and gonadectomy. In table 7, we can see the type and number of therapeutic management commonly performed by urologists except in the two cases of vaginal agenesis, which was performed by an obstetrics gynecologist.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is the most common DSD in several reports.[7-9] In fact, a study reported the frequency of CAH of as high as 72%.[8] The next most common DSD is androgen insensitivity syndrome (AIS).[9] We found similar result in our study. CAH is the most common DSD, contributing as high as 56,4% of all cases, followed AIS as the second most common DSD represents 13,5% of all DSD cases.

The patient's age at diagnosis is varied. If ambiguous genitalia are evident, most patients can be diagnosed when they are still neonates or toddlers. However, the DSD cases can also be diagnosed initially in older age groups. Usually, the presence of unrecognized or belatedly recognized ambiguous genitalia, the presence of hernia in girls, delayed puberty, and virilization for girls, primary

amenorrhea, and the absence of breast development in girls are responsible for the delayed diagnosis.[10] In this study, 48% of the cases was diagnosed when the patient is under 1 year old, 20% during toddlerhood, 8% during prepubertal period, and 23% during the pubertal period. CAH was the most common DSD observed in infants under the age of 1 year (78%). These findings similar with a number of other reports. The Rajendran report in 1995 observed the same findings, 86% of DSD cases were diagnosed in toddler period and 8,5% during pubertal period.[11] A report conducted by Joshi (2006) in 109 patients found that 57,8% cases were diagnosed during the first year of the patient's life.[9] These findings shows that the understanding and early detection of DSD cases in the multidisciplinary team in RSCM is similar to the institutions abroad.

Considering the sex of rearing, we can see that most of the DSD sex chromosome and 46 XX DSD are raised as girls (respectively 92% and 83%) while the 46XY DSD are raised as boys (61%). On the gender assignment, all of 46 XX DSD decided to become female, while gender assignment result for 46 XY DSD and sex chromosome DSD are varied.

The management of DSD poses its own challenges. Establishing a diagnosis or the type of DSD, gender assessment, and surgical or pharmacological therapy are still considered controversial issues. Therefore, the management of DSD requires a multidisciplinary approach. The team should consist of endocrinologist, urologist, anesthesiologist, geneticist, obstetrics gynecologist and psychiatrist.[6]

The urologist should always be a central member of the multidisciplinary team and usually becomes a first line consultant, especially in an institution without a DSD multidisciplinary team.[4] The urologist plays a role in the diagnostic and therapeutic management. The diagnostic management that can be performed by the urologist include anamnesis, physical examination when the patient is anaesthetized, imaging by ultrasonography and genitography, uretrocystoscopy, and laparoscopy.[6] The therapeutic management that can be conducted by the urologist are masculinizing surgery, feminizing surgery, and gonadectomy.

Physical examination under anaesthesia is required because the patients are commonly still very young so that a complete physical examination without anaeshthesia would be very difficult. Physical examination is necessary to evaluate the morphology of the external genitalia, such as the shape and size of phallus, the shape and color of the labioscrotal fold, the presence of gonads and accompanying abnormalities such as urogenital sinus.

Genitography is performed to evaluate the shape and abnormalities of the vagina and the presence of urogenital sinus and its classification. Uretrocystoscopy and colposcopy are performed to confirm the anatomical results of genitography, to verify the uterus portio, to visualize the type of urogenital sinus and its position regarding the introitus and bladder neck.[12] The type of urogenital sinus and its position regarding introitus and bladder neck is very important to determine the type of reconstructive surgery.[13] In this study, from the 12 uretrocystoscopy-colposcopy procedures performed, we found some type 1 high-confluence urogenital sinus and type 11 low-confluence urogenital sinus on the 46XX DSD and sex chromosome DSD group.

Diagnostic laparoscopy is performed to confirm the presence of non palpable gonads and the presence of Mullerian structure and to perform a biopsy of the gonad structure.[12] According to Medonca (2001), only the ovotesticular and sex chromosome DSD groups require diagnostic laparoscopy to support the diagnosis.[14] In this study, 9 diagnostic laparoscopy procedures were perfomed, 2 of which to the ovotesticular type patients, 6 to the sex chromosome DSD patients, and 1 to the AIS parients. From these 9 procedures, 3 cases of testes with gonad streak, 1 case of ovaries and testes, 2 cases of ovotestes, and 1 case of prepubertal testes with *gonadoblastoma testicular dysplasia* were found.

After the diagnostic management are completed, including anamnesis all the way to workup studies, a gender assignment involving the patient and the family is conducted by the multidisciplinary team. Complete diagnostic management are necessary before the gender assignment is conducted. One of the important diagnostic management is gonad biopsy during laparoscopy/laparotomy. In this study, 1 MGD case was managed by diagnostic laparotomy without gonad biopsy, proceded with female gender assignment and clitoroplasty. However, apparently the presence of testes was still suspected during evaluation. After a diagnostic laparoscopy with biopsy was performed, the biopsy specimen shows prepubertal testes. The patient then underwent

regender assignment, and was decided to still be a female and to undergo gonadectomy.

The therapeutic management are conducted after gender assignment. One of the therapeutic management is surgery. The purpose of surgery is to restore the anatomy and function of genitalia and to eliminate the possibility of gonadal malignancy.[4] The ideal time for surgery is still a controversial topic.[15]

Masculinizing surgery is generally more complex and requires more than one surgical procedures.[4] The usual procedures conducted in this surgery are chordae release, urethral reconstruction, and testosterone supplementation.[5] These surgical procedures should be conducted at early age to prevent the potential psychosexual and social problems to the patient and the family.[16] Chertin (2005) reported that masculinizing surgery procedures for children with an average age of 1,8 years old result in good outcomes.[16] While Denes (2009) reported the similar approach to the patient with older average ages of 8,6 $\pm$ 9,8 years old, but the better cosmetic outcome and fewer complications is found in the age group of under 2 years old.[17] In this research, there were several masculinizing surgeries conducted, including one phalloplasty, one hipospadia repair and orchidopexy, 6 hipospadia repair, and there was one planned hypospadia repair. Regarding the age during surgery, the majority of surgeries (62%) were conducted during toddlerhood, and the rest (38%) were during teenage period. In this research, there were cases of 5-alpha-reductase deficiency which required a dehydrotestosterone hormonal supplementation. However, the supply of such supplementation is not available in Indonesia and the postoperative phallus size remains undersized.

The procedures in feminizing surgery include the reconstruction of external genitalia, exteorization of vagina, and urogenital sinus repair. Normally, a refinement surgery is needed during puberty.[5] The patients' age during surgery also remains controversial. Ahmad Al Dassaoukay (2009) conducted feminizing surgeries to patients aged 6 months to 9 years old.[18] There were 15 clitoroplasty, 8 clitorovaginoplasty, 2 vaginoplasty, and 6 plans of clitoroplasty ot clitorovaginoplasty. Regarding the age during surgery, the majority (83%) of surgeries was conducted in the toddlerhood and the rest (17%) were conducted during pubertal period.

The type of germinal tumor in DSD are seminoma (testicular) or disgerminoma (ovaries) and non-seminoma.[19] The development of these tumor is almost always preceeded by an in situ neoplastic lesion (*intratubular germ cell neoplasia unclassified* (ITGNU) or gonadoblastoma).[20] The incidence of germinal tumor in DSD are varies. The first study reporting the incidence of germ-cell tumor incidence in AIS was approximated at 22% and then corrected to 5-10% in the further research.[19,20] Regarding the type of DSD, the risk of gonadal transformation into malignancy is varied depending on some number of parameters, some of them have already been identified. The highest risk was found in the group of gonadal dysgenesis (12-35%) and PAIS group with non-palpable gonad (20-30%). The lowest risk is found in CAIS and ovotesticular group (2,3%).[15,19] In contrast to the AIS group, the age during the incidence of germinal tumor in gonadal dygenesis group is generally earlier, since birth until the first year.[19] Gonadectomy is recommended in the high risk groups.[15] In this research, 4 laparoscopic gonadectomy was performed with 50% of the surgery was performed for MGD patients, 25% for AIS, and 25% for ovotesticular DSD. From anatomical pathology examination, one case of testes with gonadoblastoma testicular dysplasia was reported. No germinal tumour ever reported.

The outcome of the management of DSD, including the surgical management which can be evaluated in both short and long term, includes the anatomic cosmetic appearance, and sexual function. In this research, the data regarding the evaluation of DSD management is still unobtainable. Some studies which were conducted abroad reported diverse outcomes.

Sircilli (2010) reported that masculinizing surgery satisfied 85% of the patiens, but the complaints about the size of penis, sexual activity and urinary problems is not uncommon.[21] Denes' study (2009) reported that the anatomical shape which was cosmetically good was 42%, regular was 55% and bad was 3%. The common surgical complication is urethrocutaneous fistula and urtheral stricture which commonly requires corrective surgery.[17]

The cosmetic and functional outcome of the feminizing surgery is associated with the type of surgical procedures and the type of urogenital sinus.[18] Denes (2009) reported that feminizing surgery perfomed on paients with CAH results in good anatomical and functional results in 68% of the cases, and there were 21% surgical complication

including bleeding, glans necrosis and stenosis of the vaginal introitus.[22] Ahmad Al Dassoukay (2009) reported other complications such as urinary incontinence, besides the ones previously discussed.[18]

CONCLUSION

The majority case on RSCM's DSD profile was CAH. The management of DSD has been conducted by multidisciplinary team. The profile management encompasses a thourough evaluation including anamnesis, physical examination, while the patient is anaesthetized, chromosome analysis, laboratory examination, radiologis imaging, and other additional management. The management is then preceeded by a gender assignment. The gender assignment is held by the multidisciplinary team, involves the patient and family. The urologist becomes important element of this team, regarding their role in diagnostic efforts, including physical examination with or without anaesthesia, uretrocystoscopy-colposcopy and diagnostic laparoscopy along with gonad biopsy. The diagnostic management, including the gonad biopsy, should be completed thoroughly before conducting a gender assignment.

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