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Disorders of Sex Development Management, A Report of Single Centre Experience in Indonesia

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Abstract

Disorders of Sex Development (DSD) include a group of congenital conditions associated with atypical development of internal and external genital structures. Management of DSD is challenging especially if identified at later age, since the dilemma in gender alteration and decision creating a complexity of problems within the families. DSD management is problematic without specialized team management, these conditions are often unrecognized and their medical management is not considered to be a hospital priority. We established a Multi Discipline Team (MDT) at our centre, in collaboration with Dr. Kariadi provincial referral hospital and Faculty of Medicine Diponegoro University, for more than 2 decades with total of 1039 recruited patients. This MDT is the only team from our centre in Indonesia that manages DSD cases from basic laboratory examination including hormonal and genetic analysis as well as physical examination and psychological assessment. The MDT can play a critical role in creating an atmosphere of dedication to the health and welfare of children born with DSD, as well as to their families.

Keywords: Disorders of Sex Development, Multi Discipline Team, Indonesia

Introduction

Disorder of Sex Development (DSD) is defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical (Hughes et al., 2006). The frequency of atypical genitalia may be as high as 1:300 live births, but the birth prevalence of a condition that may lead to DSD condition on expert examination may be as low as 1 in 5000 births (Ahmed et al., 2016). The older terms of Disorder of Sex Development (DSD) were hermaphrodite, intersex or ambiguous genitalia which may be recognized at prenatal ultrasonography imaging, immediately after birth, or later in life. According to the Chicago Consensus conference in 2006, DSD are classified into three categories: sex chromosome DSD; 46,XX DSD; and 46,XY DSD (Hughes et al., 2006). Patients with disorders of sex development may present with wide range of phenotypes; from ambiguous genitalia, absence of secondary sex characteristics development, primary amenorrhea, hypospadias, clitoromegaly to a complex congenital malformation, such as cloacal extrophy (Arboleda, Sandberg and Vilain, 2014).

The mechanism of sex development is the process of sex differentiation of the bipotential gonad into either a testis or an ovary. Further development is the development of sex-specific reproductive tracts that regulated by hormones secreted by the testis or ovary (Arnold, 2017). The regulating pathway of sex development involves the complex interaction of genes and their products.

However, any endogenous and exogenous influence at sex development will result in a wide spectrum of sex differences (Hiort, 2017).

Sex assignment or gender decision is one of the most essential aspects of human development and social life. Comprehensive management such as MDT is needed to improve quality of life of DSD

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patients. A national protocol for management of DSD patients in Indonesia is not yet available, hence proper diagnosis is infrequent. Perhaps this is caused by lack of awareness of medical personnel, lack of priority on genetic disease as well as genital ambiguity and minimal diagnostic facilities and expertise in the country. In managing these patients, having families connected with our MDT as early as possible will ensure that we have better management and treatment strategies.

Management of DSD in Indonesia

Indonesia has 34 provinces with total population of 270.7 million in 2019. Semarang is the capital of Central Java province with 1.8 million inhabitants and has an area about 374 square kilometers. Population in the city is predominantly Javanese with significant Chinese and some Indonesian tribes from whole Indonesia. Multidisciplinary team with a holistic team-oriented approach to manage DSD with psychological support for patients and their families is only available in Semarang (Listyasari et al., 2017). In order to determine the managements and medical decision-making in patients with DSD, laboratory analysis is very helpful that can lead to an etiological diagnosis of DSD. Although, the diagnostic facilities are usually limited only in research centre or provincial referral hospital, some genes can be detected in our centre using simple molecular techniques. Advanced molecular technique using massively parallel sequencing for DSD gene panel can be done with collaborations from overseas.

MDT has been established in 1989, so far it is the only available team in Indonesia. The members are from Dr. Kariadi Hospital and Faculty of Medicine Diponegoro University (FMDU)/National Diponegoro University Hospital, which consists of specialists from various departments: urologist, plastic surgeon, gynaecologist, endocrinologist, andrologist, anaesthesiologist, medical geneticist including genetic counsellor, psychiatrist, pathologist, psychologist, legal medicine and religion leader. All patients were analysed for all aspect from clinical to laboratory examination. When all data were ready, bimonthly multidisciplinary meetings for case discussion of about 5-10 cases were carried out. All data and samples were kept for further used, especially for gene mutation analysis. Clinical management were done by each specialist of the team members. Surgery was considered carefully for children cases with informed consent from parent. Regardless of any form of surgery, the gender identity should be decided first by cytogenetics and psychosocial analysis.

Patients admitted to the division of Human Genetics, Centre for Biomedical Research (Cebior), Faculty of Medicine Diponegoro University were recorded appropriately since 2004. They were analysed for physical examination (including Prader or Quigley stage), family pedigree, karyotyping, hormonal assays (mostly for testosterone, FSH, LH, 17OHP, cortisol depending on the suspected diagnosis), psychosocial analysis and genetic counseling. Other examination such as ultrasonography, X ray, Cystoscopy, HCG tests and mutation analysis was also carried out for selected cases (see table 1).

Table 1. Clinical evaluation sheet

Subject number/ MR code	Detail
Name	
Date of birth	
Age (years)	
Address	
Telephone number	
Gender	
Karyotype	
Weight (kg)	
Length (cm)	
Dysmorphology	
Quigley stage	
Prader stage	
Urethrogenital swelling	
Labio/scrotal fusion	
Phallus length (cm)	
Chorda	
Localization meatus urethrae	
Perineum (one or two endings)	

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Gonads size (ml) /localization
Hyperpigmentation
• Body hair
• pubic hair
• axillair hair
• chest hair
Ultrasonographic
X Ray/ Cystoscopy
Blood sample, date
Hormonal data
hCG-test, date
Additional data
Photograph of the genital
Pathology/Biopsy available
Surgery, date
Medication
Father Height (cm)
Mother Height (cm)
Pedigree
Mutation analysis
Psychosocial analysis
Presumptive diagnosis
Recommendation

Outcome of DSD management and discussion

We have collected 1039 DSD patients (see table 2) from all over Indonesia for more than 2 decades, majority of which was from central Java province. In the past, patients came for medical consultation when they were already adults. The reasons for seeking our expertise were primary amenorrhea, planning to get partner, infertility, gender identity issues as well as failure of full penetration in sexual intercourse. Recently many newborn babies with DSD was referred by clinician or was brought by their parents themselves to our hospital for sexual assignment and further management. This paradigm may because of our endorsement through the young physicians with seminar, conferences, publication in social media and the most important is the availability of MDT.

Table 2. Total of DSD patients admitted to our center since 2004 to 2019 according to the Chicago Consensus

Type of DSD	Number of cases	Percentage %
46,XY DSD	778	75
46,XX DSD	187	18
Chromosomal DSD	74	7
Total	1039	100

Majority of our 46,XY DSD cases were Unknown Male Undermasculinization (UMU) with specific hormonal finding such as normal value of testosterone, FSH and LH. This group has shown various diagnoses that can be confirmed using advanced molecular techniques for mutation analysis (Eggers et al., 2016; Juniarto et al., 2016; Ayers et al., 2017). Hypospadias (mild DSD) with various type of abnormalities (pineal, scrotal and perineal) were quite frequent especially in children from the rural areas that may caused by exogenous influence such as the routine used of mosquito coil (mosquito-repelling incense) as estrogen disruptor (Kim et al., 2005). Further research is needed for possible endogenous and exogenous factors including de novo gene mutation. The majority of confirmed cases of Androgen Action Disorders by Androgen Receptor (AR) gene analysis were Androgen Insensivity Syndrome (AIS) both for Partial AIS and Complete AIS (see figure 1). The smallest numbers of 46,XY DSD cases were Gonadal dysgenesis (GD) with specific hormone value of high FSH and LH and low testosterone. However sometimes we found very difficult cases with familial GD similar like PAIS but no AR gene mutation found to have *NR5A1* mutation using massively parallel sequencing (Eggers et al., 2015).

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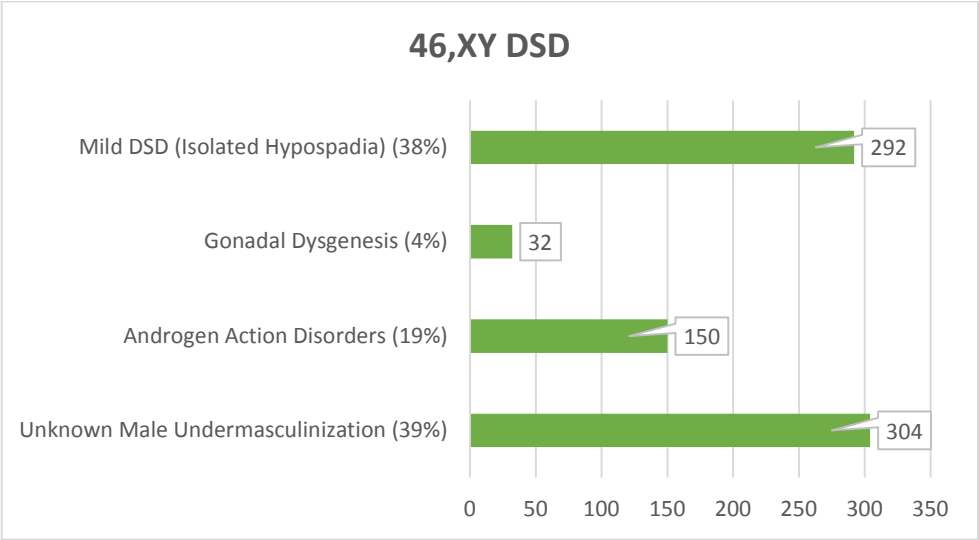

Figure 1. Distribution of 46,XY DSD patients

The majority of the cases of the next classification 46,XX DSD group were Congenital Adrenal Hyperplasia (CAH) (see figure 2). These cases were late identified because there was no newborn screening in Indonesia and lack of availability of specific medication (hydrocortisone and fludrocortisone). Only the past 5 years hydrocortisone was made available and covered by national health insurance, since then many babies with CAH could survive and female gender decision was decided. Defect in Mullerian development such as Mayer Rokitansky Kuster Hauser (MRKH) was second most common of 46,XX DSD, they presented with primary amenorrhea or failure of complete penetration during sexual intercourse because of short vagina. Advanced molecular analysis should be proposed to confirm the gene mutation (Backhouse et al., 2019).

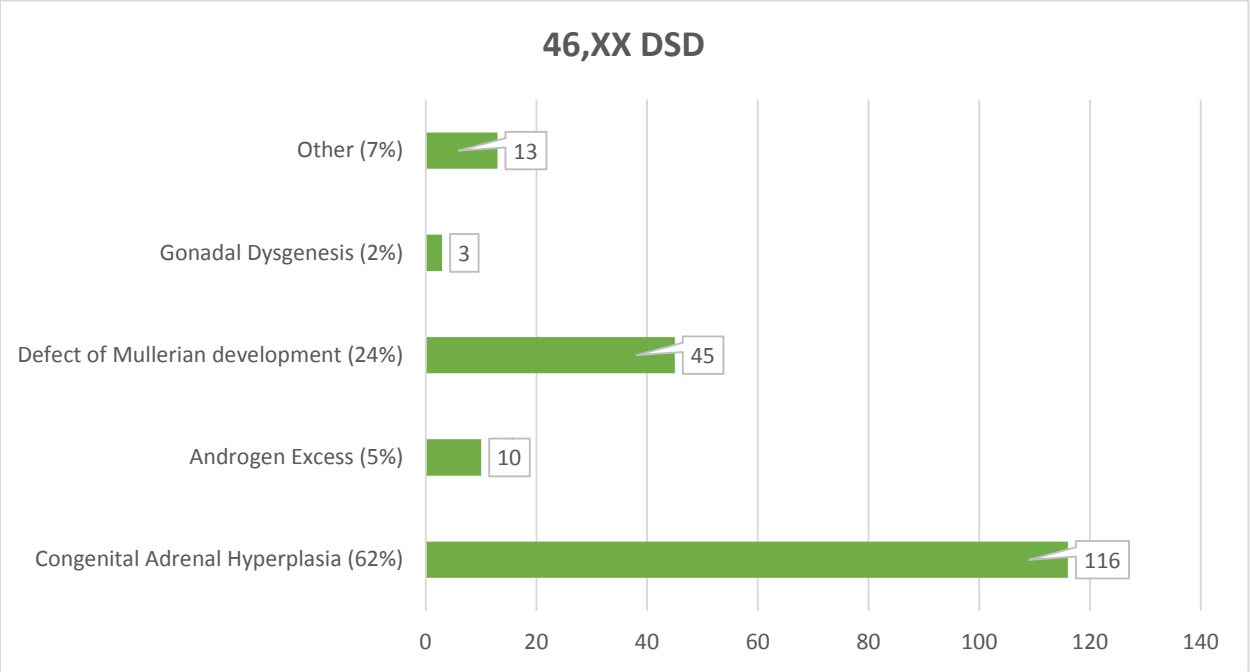

Figure 2. Distribution of 46,XX DSD patients

Majority of cases under group Sex Chromosome DSD were Turner syndrome and its variant (see figure 3). However for 45,X mosaic with 46,XY should be given more attention and care. Ultrasonography imaging to identify the position, size and type of the gonad is very important. Biopsy or removal of the gonad may be necessary to avoid malignancy (Wolffenbuttel et al., 2016; Spoor et al., 2018).

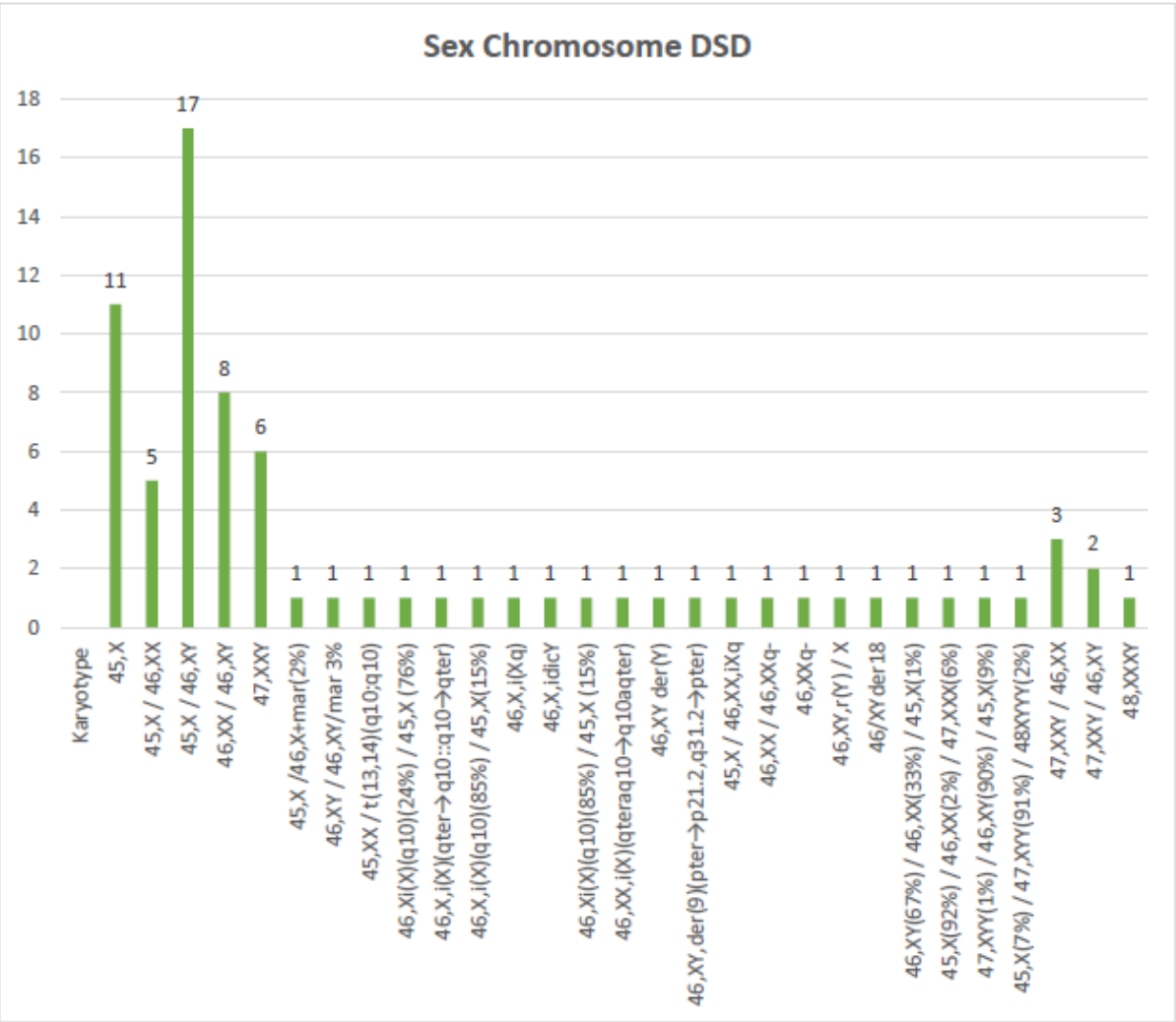

Figure 3. Distribution of Sex Chromosome DSD

The management of disorders of sex development (DSD) has been given minimal financial support by government public insurance that caused the delay of diagnosis. The dilemma was when the patient and parent found that their choice of gender and sexual rearing have been incorrect in later life, this was partly because clinicians have not assigned the gender at birth. The identification of the genetic causes of DSD will provide diagnosis and assist with clinical management of DSD, and ultimately to improve outcomes for children and adults affected by DSD. MDT should be offered for an optimal long-term outcome and for helping patients in diagnosis, gender assignment and to improve quality of life. In developing country with lack laboratory facilities chromosome analysis is the first line to lead the possible diagnosis and sex assignment, consequently at least cytogenetic laboratory should be provided in 34 provincial hospital of whole Indonesian archipelago.

Conclusion

There were different causes of ambiguous genitalia in newborn, but the most common

causes in our observation were CAH in females and PAIS in males, while frequent chromosomal DSD was Turner syndrome and its variant of X chromosome abnormality. Overall of our long term MDT found that many cases came to our centre were hypospadias, congenital adrenal hyperplasia (CAH) and Androgen insensitivity (AIS), even though UMU with broader diagnosis were actually more common than AIS. Therefore, further study with advanced molecular technique to elucidate the certain diagnosis and pattern of inheritance should be carried out. The availability of our MDT and genetic counselling clinic in our centre encourage parent or patient to come for medical consultation earlier, thus psychosocial distress and stigmatization in the community can be minimized. The management of DSD has improved sufficiently, large number of adult DSD has already well defined and ended with happy life.

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