

Hospital-Based Study: Interventions for patients with Disorders of Sex Development (DSD) in National Reference Hospital, South Sumatera Region, Indonesia

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2 A Hospital-Based Study: Interventions for Patients with Disorders of Sex Development (DSD) in National Reference Hospital, South Sumatera Region, Indonesia

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Abstract

Introduction

Disorders of Sex Development (DSD) is a term used to describe a congenital condition where sex chromosomes, gonads, and or anatomy of a person are atypical. It is estimated to affect 1:4,500 people worldwide with varied clinical findings, hence the integrated and diverse interventions.

Objective

This study wished to observe the many interventions DSD patients received in Dr. Mohammad Hoesin Hospital as one of the national reference hospitals in Indonesia for South Sumatera region.

Methods

Medical records of 173 patients with clinical findings in accordance with DSD spectrum during 2013-2017 was observed in order to identify both surgical and medical interventions applied.

Results

Sixty two patients were diagnosed of having hypospadias (35.84%), making it the most common clinical finding among DSD patients in this hospital. Surgical intervention was the most favored intervention, with 155 patients (89.6%) underwent various surgeries, ranging from urethroplasty to vaginoplasty and many more. Five patients (2.9%) were treated with either hydrocortisone and flornidol, or both. One patient diagnosed with Congenital Adrenal Hyperplasia (CAH) had both surgical and medical intervention.

Conclusion

DSD gives a wide phenotypic spectrum, making its management both challenging and complicated. Surgical, medical, and or a combination of both are the indispensable interventions when dealing with DSD patients. Study focusing on psychological intervention for DSD patients is further needed.

Keyword: Disorders of Sex Development, DSD, surgical, medical, intervention.

Introduction

People presenting with ambiguous genitalia were formerly called by terms such as 'intersex', 'hermaphroditism', and or 'sex reversal'. However, these terms have been replaced with Disorders of sex Development (DSD) since the Chicago Consensus in 2006.¹ Chicago Consensus also divided DSD into three categories: (1)Sex chromosomes DSD, (2) 46, XY DSD, and (3) 46, XX DSD.

Disorders of sex Development (DSD), is a congenital condition in which the developments of chromosomes, gonads, or anatomy is atypical.² Some of these conditions give obvious signs

or clinical findings that it can be screened at birth, such as undescended testicles.³ While some might be detected later in life due to its subtle phenotypes. Take for example, delayed or absence puberty, and infertility.

The incidence of newborn with ambiguous genitals varied within countries. It ranges approximately from 1:2,000 to 1:4,500 worldwide.⁴ Ambiguous genitals are considered as a troublesome condition that causes distress in families. It leads to questions about one's sex identity and gender identity. Therefore it is important to realize that sex does not determine a person's gender identity. Sex is more towards the biology of the external and internal genital organs, while gender depends on how an individual determines his or her own identity.⁵ Patients with ambiguous genitals confer various clinical findings that are not consistent to only one field of medical science, leading to interdisciplinary approaches from multiple experts. DSD patients often need long-term management with a variety of therapies including surgery, medical treatment, and psychotherapy.^{6,7} Given the large options of interventions, this study aims to identify interventions given to DSD patients in one of the national reference hospitals in South Sumatera region, Indonesia.

Methods

All individuals presenting with clinical findings consistent with DSD criteria during the year 2013-2017, were included in this study. All the patients had been examined thoroughly and been clinically diagnosed by competent in-charge doctor in Dr. Dr. Mohammad Hoesin Hospital. As many as 173 patients were then deemed as participants in the study. Medical records of these patients were then observed to see types of intervention these patients were receiving. Any surgical and medical treatment related to the condition were noted.

Results

There were 173 patients that were included this study, with various clinical findings, as it can be seen in Table 1. The most commonly found clinical finding was hypospadias (35.84%), that belongs to 46, XY DSD based on the Chicago Consensus.

At admission, almost every DSD patients were having a defined sex where most of them were male (84.4%). Only one participant was presenting with undetermined sex during admission. Mean while, age wise, majority of the participants were in their late-childhood, which is around 6 to 12 years old. Table 2 depicted patients' demographic characteristics, which were sex and age.

Table 1. Distribution of DSD Patients Based on Clinical Findings

Clinical Findings	n	%
Hypospadias	62	35,8
UDT Bilateral	11	6,4
UDT Unilateral	15	8,7
Hypospadias + UDT Bilateral	1	0,6
Hypospadias + Chordee + UDT Bilateral	1	0,6
Hypospadias + Chordee	23	13,3
Hypospadias + Chordee + UDT Unilateral	2	1,1

Hypospadias + Chordee + Fistula Uretrokutan	1	0,6
Chordee	1	0,6
UDT Unilateral + Ca Testis Intraabdomen	1	0,6
CAH	1	0,6
CAH + Hypospadias + Clitoromegali	1	0,6
CAH + Hypospadias + Micropenis	1	0,6
CAH Non Klasik + Clitoromegali	1	0,6
CAH Salt Wasting + Clitoromegali	1	0,6
CAH Salt Wasting	3	1,7
Hypospadias + Fistula Uretrokutan	6	3,5
Hypospadias + Fistula Uretroskrotal	3	1,7
Hypospadias + UDT Unilateral + Fistula Uretrokutan	1	0,6
Fistula Uretrokutan	4	2,3
Fistula Uretrokutan + Chordee	2	1,2
Burried Penis + Micropenis	1	0,6
Scrotum Bifida	1	0,6
Hypospadias + Scrotum Bifida	1	0,6
Fistula Rectovagina	1	0,6
Agenesis Vagina	2	1,2
Agenesis Vagina + Amenorrhea Primer + Problems with Breast Development	1	0,6
Agenesis Vagina + Hematometra + Hematokolpos	1	0,6
Agenesis Vagina + Cyst Dermoid Dextra	1	0,6
Agenesis Vagina + Agenesis Uterus + Amenorrhea Primer	1	0,6
Septum Vagina Transversum + Hematometra + Infertil Primer	1	0,6
Non Patent Tuba Bilateral + Mioma Uteri	1	0,6
Hipertrofi Labia Minora Dextra	1	0,6
Obtruksi Azoospermia + RT Prostat Not Palpable + Infertil Primer	1	0,6
Swyer Syndrome + Streak Gonad + Amenorrhea	1	0,6
Turner Syndrome + Streak Gonad + Hipoplasia Genitalia Interna	1	0,6
Elongatio Colli + Mass in Vaginal Meatus	1	0,6
Agenesis Vagina + Stenosis Ring Neovagina	1	0,6
Septum Vagina Transversum + Mioma AP Dextra	1	0,6
Agenesis Vagina + Hipoplasia Uterus	1	0,6
Agenesis Vagina + Sinekia Labia Minora	1	0,6
Sinekia Labia Minora	1	0,6
Dysgenesis Corpus Callosum + Amenorrhea Primer	1	0,6
Hipoplasia Uterus + Polisistik Ovarii + Uterus Bicomu	1	0,6
Hypospadias + Penis Deviation	1	0,6

Hypospadias + Burried Penis	1	0,6
Hypospadias + UDT Bilateral + UDT Unilateral	1	0,6
UDT Unilateral + Micropenis	1	0,6
Burried Penis	1	0,6
Ovulatory Dysfunction + Precocious Puberty	1	0,6
UDT Bilateral + UDT Unilateral	1	0,6
Total	173	100

Table 2. Distribution of DSD Patients Based on Demographic Characteristics

Demographic Characteristics	n	%
Age		
<i>Newborn</i> (0-14 days old)	1	0,6
<i>Babyhood</i> (2 weeks - 2 years old)	17	9,8
<i>Early-childhood</i> (2-6 years old)	48	27,7
<i>Late-childhood</i> (6-12 years old)	68	39,3
<i>Puberty</i> (13-17 years old)	11	6,4
<i>Adolescence</i> (>18 years old)	28	16,2
Sex		
Male	146	84,4
Female	26	15
<i>Undetermined</i>	1	0,6

As it has been mentioned in the method section, all surgical and medical treatment related to the DSD was taken into account. Data showed that as many as 155 DSD patients during 2013-2017 had a surgical intervention (89.6%), while five patients (2.9%) were medicated using particular drug related to the case. Only one patient underwent surgery and was being medicated as well, as it can be seen in the following Table 3 below. The rest (6.9%) did not have any surgery and or medication due to various reasons.

Regarding the surgical interventions, there were 28 types of surgery conducted to DSD patients based on their clinical findings. Among them, Urethroplasty ranks the highest with 65 patients (41.9%), followed by orchidopexy (12.3%). Other types of surgery as one of the interventions identified in DSD patients can be seen in table 4.

From five patients that received medical treatment, four were treated with a drug combination of hydrocortisone and fludrocortisone. One patient was medicated with hydrocortisone, and one patient underwent both surgical and medical treatment. This patient had vaginoplasty and clitoroplasty along with hydrocortisone and fludrocortisone treatment.

Table 3. Distribution of DSD Patients Based on Interventions

Interventions	n	%
Surgical	155	89,6
Medical	5	2,9
Combination between surgical and medical	1	0,6
Without intervention	12	6,9
Total	173	100

Table 4. Distribution of DSD Patient Based on Each Interventions

Interventions	n	%
Surgical		
Urethroplasty	65	41,9
Orchidopexy	19	12,3
Chordectomy	13	8,4
Trachelectomy	1	0,6
Neovagina	1	0,6
Salphingoforectomy	1	0,6
Histerectomy	1	0,6
Repair Fistula	12	7,7
Exision septum vagina	1	0,6
Herniotomi	1	0,6
Repair MAGPI	6	3,9
Diagnostic Laparoscopy	1	0,6
TURED	1	0,6
Repair burried penis	1	0,6
Insicion sineychia labia minora	1	0,6
Dorsumsiccion	1	0,6
Laparotomy	1	0,6
Transoburator tape	1	0,6
Urethroplasty + chordectomy	15	9,7
Urethroplasty + web penis incision	1	0,6
Urethroplasty + orchidopexy	1	0,6
Orchidopexy + circumsition	4	2,6
Orchidopexy + herniotomy	2	1,3
Repair fistula + circumsition	1	0,6
Neovagina + himenectomy	1	0,6
Neovagina + nastomosis resection + vaginoplasty	1	0,6
Neovagina + anastomosis resection + laparotomi	1	0,6
Medical		
Hydrocortisone	1	20
Hydrocortisone + fludrocortisone	4	80
Combination between surgical and medical		
Clitoroplasty + vaginoplasty and hydrocortisone + fludrocortisone	1	100

Discussion

In this study, patients were mostly in their late childhood and early childhood. It is similar with another study conducted by Juniarto et al in 2016 where majority of DSD patients in Semarang were also in their early and late childhood.⁸ This phenomenon was probably related to circumcision timing. Circumcision is a common practice in Indonesia held for boys aged 5 to 12 years old.⁹ This could also be an explanation why hypospadias was the most commonly identified clinical finding in this study. Since most DSD patients admitted to Dr. Mohammad Hoesin Hospital was males, it is only normal that these patients also went through circumcision when they were in either early or late childhood years. Some patients in this study were known to have their diagnosis after their external genitals being examined by doctors before the circumcision procedure was performed.

Some of DSD phenotypic spectrum are assessable at birth, leading to an early screening and early intervention. However, only one patient was diagnosed as DSD during newborn period in this study. A study in Semarang by Ediati revealed that many patients, families, and even medical workers who are not aware that DSD is manageable.¹⁰ This raises a concern for increasing the awareness about DSD for both community and health workers in Indonesia, including South Sumatera. The better awareness, the earlier DSD patients can be identified and diagnosed, hence the early appropriate medical assistance as well.

Some studies showed CAH as their most profound DSD, whereas this study found hypospadias as its prominent clinical finding. Hypospadias itself is one of the most common male external genitals congenital abnormality.¹¹ It is also a multifactorial condition, meaning it is caused by many factors, say genetics and environmental, or combination of both. Studies abroad like one conducted by McCann-Crosby in 2016 stated that CAH is the most commonly found DSD.¹² Yet some cases of CAH could also have hypospadias as one of its clinical manifestations.¹³ Thus it is quite likely that those hypospadias cases identified in this study are clinical manifestations of CAH, especially the penoscrotal hypospadias.

It is also known that clinical findings of CAH are very diverse, ranging from phallus enlargement to almost total masculinization.¹³ This would explain why only 8 people were recorded as CAH patients with following diagnosis: CAH (0.6%), CAH with hypospadias and clitoromegaly (0.6%), CAH with hypospadias and micropenis (0.6%), non-classical CAH with clitoromegaly (0.6%), salt wasting type CAH (1.7%), and salt wasting type CAH with clitoromegaly (0.6%).

A multidisciplinary team involving experts from various background is necessary in handling DSD cases. The multiple experts involved lead to diverse interventions as well. This study recorded these following interventions: surgical, medical, and a combination of both surgery with medical.

Twelve out of 173 patients (6.9%) did not undergo any interventions due to various reasons. Many refused the surgical treatment being offered. This could be caused by lack of comprehension about the condition. Education about DSD and its treatment should really be increased among patients and families affected.

Surgical intervention comes first among other interventions (89.6%) in Dr. Mohammad Hoesin Hospital, Palembang. Ambiguous genitals give rise to social emergency where one is prone to experience confusion about one's sex and gender identity. All these confusions could lead to impaired social function and mental problems, both in patients and families. Corrective and or sex assignment surgery can help solve the issue.

In this study there was only one patient who received a combination of surgical and medical. The patient was diagnosed with CAH. The striking ambiguous genitalia finding in this patient was clitoromegaly, hence the clitoroplasty and vaginoplasty intervention. Clitoroplasty is only performed on patients with severe clitoromegaly (prader III-IV).¹⁴ Aside from the surgical intervention, the patient also treated with drug combination of fludrocortisone injection and hydrocortisone tablets.

Out of 173 patients, one hundred and fifty six patients had surgical intervention. From 156 that underwent surgery, 128 (82%) had single surgery, while the rest had multiple surgery. Numbers of surgery were based on the patients' needs, often caused by the various clinical findings they had. As many as 82 patients were treated with urethroplasty with multiple approaches. Most had simple urethroplasty, but some had urethroplasty with chordeectomy (0.9%), urethroplasty with orchidopexy (0.6%), and urethroplasty with webbed penis incision (0.6%). These interventions are in line with the distribution of DSD patients based on their clinical findings (table 1), where hypospadias and hypospadias with chordees ranked first and second among other clinical findings.

The goal of hypospadias therapy is to make the penis function normally during intercourse, reposition and / or make the urethral mouth, reconstruct the shape of the penis, and to minimize complications.¹⁵ Therefore, urethroplasty is the main choice in hypospadias therapy. Chordee is also commonly found in conjunction with hypospadias, like it was found in this study. The more proximal hypospadias caused the distal end of the penis to be strained and causing a chordee.¹⁶ Therefore, chordeectomy is also done simultaneously with urethroplasty in order to bring the penis straight back. Meatal Advancement-Glanuloplasty (MAGPI) is also one of the favoured operative intervention in glanular and coronal hypospadias.¹⁷ However, only 3.8% of the patients in this study were treated with MAGPI since majority was diagnosed with penoscrotal hypospadias. Orchidopexy also has a fair distribution among the results obtained (12.2%). This is supported by the distribution of testicular undescended distribution data (UDT) among patients in the study. Orchidopexy needs to be done because of the increased risk of malignancy in UDT or cryptorchidism patients.¹⁸

Clitoroplasty and vaginoplasty were performed on CAH patients with clitoromegaly, aiming to reconstruct the external genitalia so that it looks normal both anatomically and physiologically.¹⁹ In his study, Göllü mentioned that the neovaginal procedure with the technique of making a new vagina from the colon (colovaginoplasty) is better because the colon has the right diameter and length, and has self-moistening ability. Three patients with vaginal agenesis were given neovaginal operative therapy (1.8%).

Of the 173 patients who were recorded, only five patients were given medical therapy after being identified. Truth is, almost all patients undergoing operative therapy also get medical therapy. However, after further identification, the provision of medical therapy given is symptomatic and to prevent post-operative complications, not related with DSD. Therefore, it is not included in this study.

In CAH patients with 21-hydroxylase deficiency (95% of CAH cases), the adrenal gland is not able to yield cortisone so that the synthesis of adrenal hormones is being shifted to the androgen pathway. This leads to virilisation to happen. Aldosterone (mineralcorticoid) production is confirmed to be deficient in approximately 75% of these cases.²⁰ Steroids such as hydrocortisone given to CAH patients aims to reduce virilization by suppressing ACTH

stimulation.²¹ Hydrocortisone was chosen as CAH therapy regimen because of its physiological similarity to natural glucocorticoids (cortisone), hoping to minimize the possible side effects.²²

Combination of hydrocortisone and fludrocortisone (21-acetyloxy-9 α -fluorohydrocortisone) has also been shown to be effective in the treatment of salt wasting type CAH patients, given that 21-OHD patients need replacement of mineralocorticoid deficiency.²³ Fluorohydrocortisone has physiological action similar to hydrocortisone, however, it is more useful in maintaining electrolyte balance, where fluorohydrocortisone works in the distal tubule in the kidney to increase the intake of sodium ions from tubular fluid to plasma, and increase excretion of potassium and hydrogen ions.²⁴ Fluorohydrocortisone also decreases plasma renin activity and helps suppress ACTH, which in turn will also help in controlling virilization without adding glucocorticoid doses.²³ However, in the long term, the effects of salt retention from hydrocortisone and fludrocortisone can cause hypertension in CAH patients.^{25,26}

Only one DSD with a clinical diagnosis of salt wasting type CAH from 173 patients who received both surgical and medical intervention. Patient was an eight-year-old girl who complains enlargement of the phallus due to virilization, which is a clinical manifestation of CAH. In this case, the right choice of surgical treatment is clitoroplasty and vaginoplasty with the aim of reconstructing the external genitalia in female patients, especially if experiencing severe levels of virilization.¹³

Conclusion

Dr. Mohammad Hoesin Hospital as one of the national reference hospitals in Indonesia is a house for many DSD cases spread through out South Sumatera region. Being prone to be undetected and underdiagnosed, DSD continues giving challenges to those work on the cases. Its clinical findings are ranging from ambiguous external genitals to those with internal genitals involvement. Such cases need a comprehensive management and interdisciplinary approach, leading to various interventions, namely surgical, medical, or a combination of both.

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