

Geographical Variations of Disorders of Sex Development (DSD) in South Sumatera Region

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ABSTRACT

Background

Disorders of Sex Development (DSD) is a condition where the development of sex chromosomes, gonads, and/or one's anatomy is atypical. Its causes are often due to genetic mutations, although some are also linked to environmental risk factors. These multiple aetiologies lead to varied clinical findings, ranging from obvious ambiguous genitals to subtle ones in different regions worldwide, signalling a hint of geographical variability.

Objective

This study wishes to observe the variations of clinical findings of DSD patients geographically in South Sumatera.

Methods

This was an observational study using patients' medical records in RSUP Dr. Mohammad Hoesin Palembang. Both inpatients and outpatients during five-year period span (2013-2017) with clinical findings suited DSD criteria based on Chicago Consensus in 2006 were included in this study.

Results

One hundred and forty nine patients from cities and regencies in South Sumatera province and other provinces like Jambi, Lampung, Bengkulu, Bangka-Belitung, and even Riau were included in this study. Among sixteen clinical findings identified, hypospadias ranked first (59.06%), both in general, and in each regions as well. When set by side with other regions, Palembang city as the capital city of South Sumatera province displays twelve out of sixteen clinical findings documented in this study, showing a lot more variety.

Conclusion

Every regions show difference clinical findings. Some regions housed clinical findings that were not found in other regions. However, hypospadias is the most commonly found clinical findings in all regions. It is suspected due to its correlation with certain environmental risks, that the occurrence of it becomes rather often, compared to other DSD conditions. Future studies considering risk factors involvement in order to elucidate both differences and similarities found in each regions are strongly suggested.

Keywords: Disorders of Sex Development, DSD, Geographical variations, South Sumatera

Introduction

Disorders of Sex Development (DSD) is a condition resulted from atypical development of sex chromosomes, gonads, and/or anatomy that is estimated to affect 1:1000 individuals per population.¹ The condition was previously known as intersex, pseudohermaphrodit, or hermaphrodite. Only after the Chicago Consensus in 2005, the term DSD began to be used, further dividing the condition into three categories: DSD sex chromosomes, 46, XX DSD, and 46, XY DSD.²

This atypical development in different levels causes a vast spectrum of clinical findings.^{3,4} In addition to its varied clinical findings, Brain et al. in 2010 also stated that clinical findings in DSD patients are tend to be found at certain age, adding more challenges to those working with the patients.⁵ The varied clinical findings are also due to its many possible causes, including both genetics and environmental factors, or a combination of both.⁶ There are DSD linked to environmental factors such as hypospadias, making hypospadias one of the most commonly found DSD, while there are cases that are solely caused by mutation in particular genes, like Congenital Adrenaline Hyperplasia (CAH).

The diversity in clinical findings also influence the process of determining DSD diagnosis. Establishing diagnosis in DSD is considered slow, the average of DSD patients are diagnosed at the age of middle or late adolescents.⁷ The DSD case in general can't be ascertained, but the incidence is estimated to be 1: 4500-5000, with an increasing trend worldwide.⁸ Despite its increment, there are tendency of different types of DSD occurring in different regions worldwide. This could also a hint of geographical variability influencing the occurrence of DSD.

However, there are not many studies trying to identify both the incidence and prevalence of DSD. Let alone studies that exploring the difference types of DSD found in each regions, signalling a geographical variability. South Sumatera as one of the biggest provinces in Indonesia is a home for RSUP Dr. Mohammad Hoesin Palembang. This hospital is one of the national reference hospitals in Indonesia, deemed to provide health care service to people reside in not only South Sumatera province, but also other provinces located in South Sumatera region, namely Lampung, Bengkulu, Jambi, and Bangka-Belitung. Despite its lack of facilities, cases of DSD from nearby regions have also been identified. Therefore, this study wished to help identify clinical findings of DSD found in each regions in South Sumatera and other

provinces nearby. It is hoped that through this study a pattern can be recognized, and some actions regarding the pattern can be conducted, whether to prevent the condition or to help improve the patients' condition.

Methods

This was an observational descriptive study with a cross-sectional design. Samples were (1) patients diagnosed both with the term DSD and/or other terms used previously such as intersex, ambiguous genitalia, hermaphrodite, pseudohermaprodite, and others. Samples could also be (2) all patients stated to belong to the DSD category or diagnosed according to the 2006 Chicago Consensus classification by competent doctors, who seek treatment and/or receive inpatient and/or outpatient care at Dr. RSUP Mohammad Hoesin Palembang. All the criteria above were for patients came during the period of January 1, 2013 until December 31, 2017 in RSUP Dr. Mohammad Hoesin Hospital, Palembang. Patients' clinical findings, address, and demographic characteristics such as age and sex when they first admitted were the variables being sought, obtained from medical records.

Results

Among one hundred and forty nine patients included in the study, majority of them were males (85.91%) when they were first admitted with only twenty one females (14.09%). No patients included in this study with unspecified gender.

Age-wise, majority of the patients came during their late childhood year, which is more than 6 years old to less than 12 years old (37.59%), followed by early childhood, which is around 2 years old to six years old. The least age group found was neonates and early infancy. Full information regarding patients' age and sex can be seen in table 1.

Table 1. Distribution of DSD patients based on sociodemographic characteristics (N=149)

Patients' Sociodemographic Characteristics	N	%
Age		
≤1 month (neonates)	3	2.01
>1 month ≤1 year (early-infancy)	3	2.01
>1 year ≤2 years (late-infancy)	10	6.71
>2 years ≤6 years (early-childhood)	39	26.17
>6 years ≤12 years (late-childhood)	56	37.59
>12 years ≤15 years (prepubertal)	9	6.04
>15 years ≤18 years (adolescenes)	5	3.36
>18 years (adults)	24	16.11
Sex		
Male	128	85.91
Female	21	14.09

Although RSUP Dr. Mohammad Hoesin is located in Palembang, DSD patients came from many other cities and/or regencies in South Sumatera and from other provinces nearby as well. Lampung, Jambi, Bengkulu, Bangka-Belitung, and Riau were the other provinces where DSD patients also came from. However, Palembang as the capital city of South Sumatera is crowned as the most populated city with 45 cases of DSD (30.20%) during 2013-2017. The rest were spread in many other regions as depicted in table 2.

Table 2. Distribution of DSD patients based on place of origin (N=149)

Place of Origin	n	%
Palembang City	45	30.20
Prabumulih City	6	4.03
Lubuk Linggau City	3	2.01
Pagar Alam City	2	1.34
Ogan Komering Ulu Timur Regency	9	6.04
Ogan Komering Ulu Selatan Regency	3	2.01
Ogan Komering Ulu Regency	4	2.68
Ogan Komering Ilir Regency	9	6.04
Ogan Ilir Regency	7	4.70
Banyuasin Regency	9	6.04
Muara Enim Regency	14	9.40
Musi Banyu Asin Regency	12	8.05
Lahat Regency	8	5.38
Musi Rawas Regency	2	1.34
Empat Lawang Regency	2	1.34
Bengkulu Province	4	2.68
Lampung Province	1	0.67
Bangka Belitung Province	3	2.01
Jambi Province	5	3.36
Riau Province	1	0.67

With sixteen clinical findings documented as listed in table 3, this study was not an exception to the theory stating that DSD has a wide range of phenotypes. Varying from the most commonly found clinical findings which was hypospadias (59.06%) to the least commonly found like Turner syndrome, hypoplasia uterus, Hypertrophy labia minora dextra, and Stenosis ring neovagina, -each with one case-, this study also shows diversity in clinical findings of DSD patients just like many other studies.

Table 3. Distribution of DSD patients based on clinical findings (N=149)

Clinical Findings	n	%
Hypospadias	88	59.06
Bilateral UDT	8	5.38
UDT Dextra	8	5.38
UDT Sinistra	6	4.03
CAH	4	2.68
Salt Wasting CAH	4	2.68
Septum Vagina Transversum	2	1.34
Agensis Vagina	7	4.70
Turner Syndrome	1	0.67
Fistula Ureterocutan	11	7.38
Stenosis Ring Neovagina	1	0.67
Amenorrhea Primer	3	2.01
Hipoplasia Uterus	1	0.67
Hypertrophy Labia Minora Dextra	1	0.67
Synechia Labialis	2	1.34
Burried Penis	2	1.34

Despite coming from different places, clinical findings found in all 149 patients in this study were varied. Besides living up to the theory where DSD is known to have a wide spectrum of phenotypes, this phenomenon could also be a proof of possible influence by geographical differences. Table 4 below provides data of each types of clinical findings and its frequency in each and every patients' place of origin. It can be seen that Palembang as the capital city of South Sumatera province is a home to many DSD cases with the most varied clinical findings, twelve out of sixteen clinical findings identified. However, of all twenty places of origins, each and every place has the same majority cases, which is hypospadias.

Table 4. Distribution of DSD patients' clinical findings based on place of origin (N=149)

Place of Residences	Clinical Findings																															
	Hypospadias		Bilateral UDT		UDT Dextra		UDT Sinistra		CAH		Salt Wasting CAH		Septum Vagina Transversum		Agenesis Vagina		Turner Syndrome		Fistula Ureterocutan		Stenosis Ring Neovagina		Amenorrhea Primer		Hypoplasia Uterus		Hypertrophy Labia Minora Dextra		Synechia Labialis		Burried Penis	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Palembang City	26	17.45	1	0.67	5	3.36	2	1.34	2	1.34	2	1.34	-	-	1	0.67	-	-	3	2.01	1	0.67	2	1.34	-	-	1	0.67	-	-	2	1.34
Prabumulih City	3	2.01	1	0.67	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-
Lubuk Linggau City	1	0.67	-	-	-	-	-	-	-	-	-	-	2	1.34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pagar Alam City	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ogan Komering Ulu Timur Regency	5	3.36	1	0.67	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	1	0.67	-	-
Ogan Komering Ulu Selatan Regency	1	0.67	-	-	-	-	1	0.67	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ogan Komering Ulu Regency	4	2.68	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Ogan Komering Ilir Regency	6	4.03	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	-	-	1	0.67	-	-		
Ogan Ilir Regency	3	2.01	-	-	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	3	2.01	-	-	-	-	-	-	-	-	-	-		
Banyu Asin Regency	5	3.36	1	0.67	1	0.67	-	-	1	0.67	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-		
Muara Enim Regency	11	7.38	-	-	-	-	2	1.34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Musi Banyu Asin Regency	7	4.70	1	0.67	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-		
Lahat Regency	6	4.03	-	-	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-		

Musi Rawas Regency	2	1.34	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Empat Lawang Regency	1	0.67	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Bengkulu Province	2	1.34	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Lampung Province	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bangka-Belitung Province	3	2.01	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Jambi Province	1	0.67	1	0.67	-	-	-	-	-	-	-	-	-	2	1.34	-	-	-	-	-	-	-	-	-	-	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Riau Province	1	0.67	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Discussion

As it can be seen in table 1, most patients in the study came during their late childhood years. A research conducted by Berglund et al. in 2016 revealed that the median age of diagnosed DSD patients was the pre-puberty age group and adolescents.⁷ This happens because in Indonesia, early childhood and late-childhood which falls in the age range of 5-12 years, is the average age of male children who will undergo circumcision procedures.⁹

This in line with some stories told by the parents where most of their chief complaints was found out where patients were taken to hospital for circumcision. Hence the physical examination on their genitals leading to the establishment of DSD diagnosis.

Other interesting fact is that the least age group found was neonates and early infancy. One of the studies conducted in Indonesia showed that the majority of new DSD cases examined their children at the age of 2 years and above or in the early-childhood.¹⁰ This can happen because information about DSD is still not widely known, both by medical professionals and common people here in Indonesia. Therefore, genital abnormalities or other signs of DSD are not recognized easily. Although recognized, often time a referral to a specialist health center has never been conducted, either because the health care provider were not aware of the condition or the patients themselves do not have information to refer themselves.¹⁰

In the sex category, the majority were male. The sex referred to here is the sex of the DSD patient when they first admitted in Dr. RSUP Mohammad Hoesin Palembang, both as inpatient or outpatient. To date, there are no specific studies focusing on the exact distribution of DSD patients' sex. Yet there are numbers of possible reasons that could explain the condition. First is because in the 46, XX DSD category, there are conditions that is caused by an androgen excess. When this condition strikes, it will be quite easy to notice some genital changes like phalus formation. Phalus found in females making the individual looks like male, lead to sex assignment as male. This phenomenon could easily be considered as one of the possible scenarios on why males are more often found than females in DSD cases.

Second one, one of DSDs that is frequently found is hypospadias. It happens exclusively in male, causing one's orificium uretra externa to be ectopically located. Hypospadias is also thought to be affected by environmental risk factors as well along with genetic mutations and polymorphism as its other many causes. The many possible underlying

cause of hypospadias making it one of the most commonly found DSD worldwide. This also explains the fact that hypospadias was found in all twenty place of origin from all 149 patients.

Second most commonly found clinical findings was undescended testicles (UDT). This is probably because UDT is believed to be a multifactorial condition as well, just like hypospadias. Both have similar risk factors like exposure to pesticides. Most samples suffering from both hypospadias and UDT did live in areas with a lot of rice fields with a high level of pesticide exposure.

Among twenty regions that served as the place of origin for participants in this study, Palembang as the capital city of South Sumatera had 45 cases of DSD out of 149 patients in total during 2013-2017. This could be because RSUP Dr. Mohammad Hoesin is located in this city, making it easy for the residents to come and visit RSUP Dr. Mohammad Hoesin should they have any health problems, including ambiguous genitals. Each regions showed varied clinical findings identified although they all possess similarity, in which hypospadias as the most commonly identified case. Explanation on how hypospadias could rank first has been described below, with possibilities of environmental exposures in each areas.

Conclusion

Palembang as the capital city of South Sumatera province where the national reference hospital is located is a home for majority of DSD cases found in South Sumatera, compared to other regencies and/or cities. Elaborative studies regarding the risk factors in each areas are further needed in order to elucidate reasons behind these geographical variations.

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