



St. Paul Hospital Millennium Medical College
Graduate Study Program

CLASSIFICATION, CLINICAL PRESENTATION AND MANAGEMENT
OF DISORDER OF SEXUAL DEVELOPMENT IN ST PAUL HOSPITAL
MILLENNIUM MEDICAL COLLEGE

Gelila Girma (Pediatrics Resident)

Addis Ababa, Ethiopia

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**CLASSIFICATION, CLINICAL PRESENTATION AND MANAGEMENT OF
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MILLENNIUM MEDICAL COLLEGE**

**A THESIS TO BE SUBMITTED TO DEPARTMENT OF PEDIATRICS AND
CHILD HEALTH, SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL
COLLEGE FOR THE PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE CERTIFICATE IN PEDIATRICS AND CHILD HEALTH**

BY: Dr GELILA GIRMA (PEDIATRICS RESIDENT)

**ADVISOR: Dr FIKIR MESERET (PEDIATRICIAN, ASSISTANT
PROFESSOR OF PEDIATRICS AND CHILD HEALTH, PEDIATRIC
ENDOCRINOLOGIST)**

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Abstract

Background: Disorders of sexual development (DSD) were defined in the Chicago Consensus, 2006 as congenital conditions in which the development of chromosomal, gonadal and anatomical sex is atypical (Rojas, 2020). There are no clear estimates of the incidence rate of subjects presenting with ambiguous genitalia at birth, and only a proportion of them present a major challenge regarding male or female assignment. There is a paucity of data on the incidence; however, it has been estimated to be approximately 1 in 4,500–5,500.

Objectives: The objective of the study was to assess classification, clinical presentation and management of DSD patients from the Pediatric Endocrine OPD in SPHMMC

Methods: A Retrospective cross- sectional study done in SPHMMC consisting source population of All pediatric age group that came to endocrinology follow up clinic of pediatrics and child health department SPHMMC

Results: This study involved a total of 54 patients, which were evaluated at the endocrine OPD in the study period. Majority (80%) of the patients presented with observation of ambiguous genital. Additional 5.6% (3) had ambiguous genital along with congenital malformations. Out of the 30 patients who had karyotype done, majority of them were found to have 46 XY DSD 21 (70%)

Conclusion and recommendations: In this study a delayed presentation of patients was observed with ambiguous genital being the most common presenting complaint. Based on these findings we recommend a meticulous genital exam of new born to be done after delivery. We also recommend to strengthen the multi-disciplinary team management of the patients. We also recommend evaluation of all DSD patients at the endocrinology unit before surgical intervention is done.

Acronyms and Abbreviations

DSD	Disorders of sexual Development
SPHMMC	Saint Paul Hospital Millenium Medical College
CAH	Congenital Adrenal hyperplasia
MGD	Mixed Gonadal Dysgenesis
17-ohp	17-hydroxypregnenolone
DHT	Dihydrotestosterone
RBS	Random Blood Sugar
EMS	External Masculinization Score
MDT	Multi-disciplinary team

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1. INTRODUCTION

1.1 Background

Sexual development is an intricate physiological process that consists primarily of the development of the uro-genital tract and reproductive system (Qiao1, 2018). In most mammals, the development of embryonic gonads (testis or ovary) is determined by the sex chromosomes and originates from a bipotential primordium. Subsequently, locally synthesized and circulating action hormones control the differentiation of genitalia. (Ruth M. Baxter, 2015). Various genetic defects have been identified in gonadal determination or hormonal biosynthesis and actions that present a spectrum of gonadal and genital phenotypes; these phenotypes are defined as disorders of sexual development (DSD) (Valerie A. Arboleda, 2014).

Disorders of sexual development (DSD) were defined in the Chicago Consensus, 2006 as congenital conditions in which the development of chromosomal, gonadal and anatomical sex is atypical (Rojas, 2020). The terminology has led to confusion regarding the incidence of conditions included. In response to the concerns regarding the outdated, confusing or shameful terms, such as “hermaphroditism”, the consensus statement recommended this new taxonomy based on the umbrella term, DSD (Lee, 2016)

There are no clear estimates of the incidence rate of subjects presenting with ambiguous genitalia at birth, and only a proportion of them present a major challenge regarding male or female assignment. There is a paucity of data on the incidence; however, it has been estimated to be approximately 1 in 4,500–5,500 (Lee, 2016).

The proper and prompt diagnosis of DSD is always challenging, given the significant heterogeneity of the clinical presentations in 46, XY DSD patients, which is imperative for gender assignment, treatment strategies, and long-term counseling for the individuals and family (Qiao1, 2018).

1.2 Statement of the problem

There is a paucity of data on the incidence of DSD; it is estimated that the overall incidence of DSD is one in 5,500. Congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis (MGD) are the most common causes of ambiguous genitalia, constituting approximately over 50% of all cases of genital ambiguity in the newborn period. (Prisca Amolo, 2019) But the incidence varies considerably among different populations.

While the Chicago consensus on DSD classification is helpful in assignment of diagnosis, the utilization of more traditional clinical skills is invaluable for initial assessment. Around 80 % of the underlying causes of DSD are not known. (Amar Y. Rawal, 2015)

St Paul Millennium Medical College is one of the largest hospitals in Ethiopia receiving an immense amount of patients from different parts of the country. It currently has more than 700 beds, with an annual average of 300,000 patients and a catchment population of more than 5 million. In accordance to this, the department of pediatrics and child health is one of the biggest in the country delivering its service in large scope. Lately, there has been an increasing influx of patients with disorders of sexual development in the hospital. Yet there are no statistics in Ethiopia that could help physicians' apprehension towards DSD.

The study mainly will assess the classification clinical presentation and management of DSD in SPHMMC where such studies are not yet undertaken. Although there are no widely available technologies that could aid in determining the etiologies of DSD, knowing the frequency of classification and clinical presentation of DSD here in Ethiopia would help immensely in patient care. In addition to this, it will create awareness among health care workers as it is thought to be poor resulting in delayed diagnosis and high morbidity and mortality. Furthermore, it will pave a way for broad researches where appropriate technologies can be utilized to classify DSD according to molecular genetics analysis.

1.3 Rationale of the Study

In Ethiopia there are currently no data on the classification and clinical presentation of DSD in Ethiopian children and adolescents. Furthermore, diagnosis and management of DSD in resource-limited settings like ours represent a major challenge. Awareness among health care workers is thought to be poor resulting in delayed diagnosis and high morbidity and mortality.

The aim of this study is to describe the base line data on classification, clinical characteristics and management of DSD attending follow up at St. Paul Millennium Medical College's Pediatric Endocrine Clinic. We hope that the study results will be used to inform future policies that will enhance the quality of care given to these patients as well as add to the of knowledge on DSD from Ethiopia. We also hope that it will show the approach of DSD patients in a resource limited set ups like ours. It will also serve as a basis for appropriate further research.

2. LITERATURE REVIEW

Sexual development is an orchestrated pathway that directs undifferentiated zygotes towards male or female destiny (Sperling, 2014). Disruption of the tightly regulated process of sex determination and differentiation can result in disorders of sexual development (DSD), defined as a state when the “development of chromosomal, gonadal or anatomical sex is atypical (Yanjie Fan1, 2017). Perceptions and the approach to the diagnosis and care of individuals with DSDs continuously change. Advances in identification of molecular genetic causes of abnormal sex with heightened awareness of ethical issues and patient advocacy concerns necessitate a reexamination of previously used terms. Terms such as “intersex,” “pseudohermaphroditism,” “hermaphroditism,” “sex reversal,” and gender-based diagnostic labels are particularly controversial. (Lee, 2016). The currently proposed term is “disorders of sex development” (DSD), as defined by congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical. (Rojas, 2020). The proposed changes in terminology are summarized in the following table.

TABLE 1 Proposed Revised Nomenclature	
Previous	Proposed
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

There are numerous modes of classification with exhaustive lists of all the possible causes of DSD. No system is perfect, and all will date as advances in molecular genetics result in improved diagnostic insight (Hughes e. A.). DSD are classified according to the alterations in the levels of sex designation: gene sex, chromosomal sex, gonadal sex, hormonal sex, ductal sex, external genitalia, secondary characters, legal assigned sex and psychological characteristics (Rojas, 2020). According to the classification proposed by

the Pediatric Endocrinology Society Lawson Wilkins and the European Society of Pediatric Endocrinology, DSD is classified as 1) DSD sex chromosomes, 2) DSD 46,XX and 3) DSD 46,XY (Rojas, 2020). Congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis (MGD) are the most common causes of ambiguous genitalia, constituting approximately over 50% of all cases of genital ambiguity in the newborn period (Prisca Amolo, 2019).

Diagnosing DSDs often requires a long and tedious process, but often it is disappointing for patients and medical professionals (Aysun Ataa, 2021). Rapid and accurate diagnosis of DSD shows urgency in terms of gender selection and case management in a newborn baby (Merih Çetinkaya, 2018). The clinical evaluation of an individual with DSD or atypical genitalia begins with evaluation of vital signs, general physical examination, description of sexual characteristics and detailed evaluation of the perineal area consisting of observation, palpation and measurement (Rojas, 2020). A complete clinical history including prenatal and family history in a multidisciplinary group assessment is necessary to achieve an accurate diagnosis (Rojas, 2020). First-line tests include measurement of 17-hydroxy- progesterone, blood electrolytes, determination of AMH and gonadotrophin levels, together with a cytogenetic study (karyotype) and an abdominal ultrasound in search of müllerian structures. Additional tests will be dependent on the results of the initial tests to guide the diagnostic suspicion. (Rojas, 2020). Many individuals with a DSD are recognized in the newborn period, when ambiguous genital development is noted on the infant's first physical examination (Lee, 2016).

There is a paucity of data on the incidence; however, it has been estimated to be approximately 1 in 4,500–5,500 (Lee, 2016). When considering all genital congenital anomalies, including cryptorchidism and hypospadias, the incidence can be from 1:200 to 1:300 (Rojas, 2020). The incidence of CAH and MGD worldwide is 1:15,000 and 1:10,000, respectively, but varies considerably among different populations (Prisca Amolo, 2019).

Worldwide, in different studies there have been different etiologies identified with variability in different populations. In a 3-year retrospective study done in Turkey which was published in 2011, 95 patients were included. Out of the 95 patients, 26 had sex chromosome DSD, 45 had 46,XY DSD and 24 had 46,XX DSD. The most common causes of DSDs were Turner's syndrome (TS), congenital adrenal hyperplasia (CAH) and androgen insensitivity syndrome (AIS). (Sema Erdogan, 2011) On the contemporary in a 9 years retrospective study done at a tertiary Hospital in India 39 patients were studied, out of which 48.7% were diagnosed with 46 XY DSD. Out of 46 XY DSD, androgen insensitivity was observed in 8 (42.1%) patients and 5 alpha-reductase deficiency in 5 (26.3%). 16 (41%) of the patients were diagnosed with 46XX DSD. CAH was the most common cause in XX DSD, being observed in 11 (68.75%) of the 16 XX DSD patients. (Jahagirdar Rahul, 2020)

There are few nationally representative data on the prevalence of DSD in Africa. A retrospective review published in 2012 of 122 Sudanese children reported that 57% (n = 69) of patients had 46 XX DSD and 37% (n = 45) had 46 XY DSD (Yasmeen Ganie*, 2016). In contrast in a review published in 2008 of 208 Egyptian children it was reported that 46 XY DSD was more common than 46 XX DSD constituting 65.9% of all cases (Mazen, 2018). The most common etiological diagnosis in sub-Saharan Africa is 46 XY DSD disorder in androgen synthesis and action, followed by ovotesticular DSD. CAH is only the third most common disorder (Yasmeen Ganie*, 2016). In a study done in Kenya in December 2019, Based on karyotype analysis, 19 (48.7%) of karyotyped children had 46,XY DSD ,18 (46.2%) had 46,XX DSD and there were 2 (5.1%) children who were diagnosed with sex chromosome DSD . Karyotype was done for 39 out of the 71 children included in the study. The most common cause of DSD identified was ovotesticular DSD (14.1 %), followed by CAH (11.3%). (Prisca Amolo, 2019).

The prevalence of DSD in the general population of South Africa is unknown (Yasmeen Ganie*, 2016). There are no clear estimates of the incidence rate of subjects presenting with ambiguous genitalia at birth, and only a proportion of them present a major challenge regarding male or female assignment.

In Ethiopia there are currently no data on the etiological diagnoses and clinical presentation of DSD in Ethiopian children and adolescents. Although there seems to be increased influx of such cases in Ethiopia, there are no data supporting this change. This study aims to assess the classification and clinical presentation of DSD in SPHMMC where such studies are not yet undertaken. Although there are no widely available technologies that could aid in determining the etiologies of DSD, knowing the clinical presentation and investigation modalities of DSD here in Ethiopia would help immensely in patient care.

3. OBJECTIVES

3.1. General objective

- To describe Classification, Clinical presentation and management of DSD patients at the Pediatric Endocrine OPD in SPHMMC

3.2. Specific objective

- To assess the characteristics of different clinical presentations of DSD among different age groups
- To assess the presumed classification of cases of DSD
- To assess the management of DSD

4. METHODS

4.1. Study area

St. Paul's Hospital Millennium Medical College in Addis Ababa is the second largest hospital in Ethiopia. The Hospital was built by Emperor Haile Selassie I in 1969 with the help of the German Evangelical Church. The hospital has over 700 beds and serves an average of 300,000 patients annually. It has a catchment population of more than 5 million. The hospital has 2800 clinical and non-clinical staff. There are more than 15 departments including the department of pediatrics and child health.

4.2. Study period

It is a 5 year retrospective study conducted from October 2017- October 2018

4.3. Study design

A Retrospective descriptive cross-sectional study design was used

4.4. Study population

Source population

All pediatric age groups diagnosed with DSD in the study period was included as a source population. The recruitment was based on the clinical criteria of DSD diagnosis.

Study population

All pediatric age groups that were newly diagnosed with DSD and/or on follow-up that fulfills the inclusion criteria.

Inclusion and exclusion criteria

Inclusion criteria

- Inclusion criteria covered all conditions described as DSD and below the age of 18 years

Exclusion criteria

- Patients that have undergone surgical correction before evaluation at the Endocrine Unit
- Patients who have incomplete chart

4.5. Sample size

All patients who were below 18 years and diagnosed with DSD were included.

4.6. Study variables

4.6.1. Dependent variable

- Classification of DSD
- Clinical presentations of DSD
- Management of DSD

4.6.2. Independent variable

- **Sociodemographic**- age, gender of rearing, religion, socioeconomic status(educational status of parents, economic status),ethnicity , place of residency
- **Clinical variables**- consanguinity, family history of similar illness, fetal/infant loss, place of delivery, referral, prenatal diagnosis, Antenatal Drug Exposure, complaints at presentation, associated comorbidities, syndromic association, physical examination
- **Modalities of diagnosis** - ultrasound, laboratory (RBS, creatinine, serum electrolytes, serum testosterone, dehydroepiandrosterone, Androstenedione, Dihydrotestosterone (DHT), 17-ohp, cortisol, karyotype

4.7. Data Analysis

All data was entered to Excel data and was cleaned for data quality. Then the data was imported to SPSS software version 26. Descriptive statistics was computed and data was presented in text, table and graphs. P value was calculated and p-value less 0.005 was considered statistically significant.

4.8. Data Processing and Management

The qualities of the data were maintained before, during and after data collection. Before data collection the check list for retrieving the data were evaluated. The medical history of the patients was also checked for completeness. During data collection the history of the patients were taken carefully without missing any

variable. After data collection the data were checked again to verify its validity and if there is problem medical history will be again reviewed.

4.9. Ethical considerations

The study proposal was evaluated and approved by the Research Ethics Review Committee SPHMMC and ethical clearance was obtained. Permission was obtained from department of Pediatrics and Child Health. Moreover, the confidentiality of the medical history were maintained and assured.

4.10. Operational Definition

1. **DSD** is defined by congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical. (Hughes, 2006)
2. Criteria for suspecting DSD include (Khana, 2019)
 - ✓ Overt genital ambiguity
 - ✓ Apparent female genitalia with an enlarged clitoris, posterior labial fusion or inguinal/labial mass
 - ✓ Apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal or penoscrotal hypospadias, mild hypospadias with undescended testis, and delayed puberty
 - ✓ Discordance between genital appearance and Karyotype
3. Due to our restricted resources, we have mostly used imaging, clinical evaluation, and karyotype for DSD classification. Thus, we determined the patients' diagnoses based on the following standards.
 - 3.1 Patient was presumed to have 46 XY DSD if the following criteria were met:
 - ✓ On physical examination - Presence of palpable gonad in the inguinal or labioscrotal folds
 - ✓ On Ultrasound, if there is absence of Mullerian structures and visualization of testicular tissue.
 - ✓ For those who could afford karyotype and specific genetic tests were used.
 - 3.2 Patient was presumed to have 46 XX, CAH if the following criteria were met:
 - ✓ On physical examination- Absence of palpable gonads and Ambiguous genital with varying degree of virilization
 - ✓ Patients with presence of hypoglycemia, hyponatremia, hyperkalemia or evidences of hypovolemia were viewed as having Salt losing CAH
 - ✓ Investigations showed elevation on the 17HOP level
 - ✓ On Ultrasound- Presence of Mullerian Structure, Absence of testes, and signs of Adrenal Hypertrophy
 - ✓ For patients who could afford it, further evidence of CYP21A2 gene mutation and karyotype were utilized.
 - 3.3 Patient was presumed to have Sex chromosome DSD if the following criteria were met:
 - 3.3.1 Turner Syndrome was clinically suspected for those who present with
 - ✓ Short stature, developmental delay
 - ✓ Dysmorphic features such as webbed neck ,redundant nuchal skin, Low posterior hairline, low set ears, narrow and high arched palate
 - ✓ Shield chest with widespread nipples
 - ✓ Congenital lymphedema

- ✓ Skeletal abnormalities such as cubitus valgus, Congenital hip dislocation, Scoliosis, short metacarpals, defective dental development
- ✓ Congenital heart disease mainly Coarctation of aorta, Bicuspid aortic valve, aortic stenosis, and mitral valve prolapse
- ✓ structural renal anomalies like horseshoe kidneys
- ✓ infertility, primary amenorrhea

Turner syndrome was confirmed karyotypically for those patients who could afford

3.3.2 Klinefelter syndrome was clinically suspected in patients with different degrees of genital ambiguity, delayed puberty, gynecomastia, or tall stature, and karyotypically confirmed in patients with 47 XXY or its variants.

3.3.3 Or if the patient couldn't be classified under 46 XY or 46 XX category

4. **Micropenis**- A stretched penile length less than 2.5 standard deviations below mean for age group is considered as micropenis (Hatipoglu, 2013)
5. **Cliteromegaly**- is defined by clitoral length or width above mean + 2SD or clitoris length of above 1 cm. (Alev, 2010)
6. **Genital Ambiguity for an apparent male** – Evaluation of a phenotype of an apparent male with ambiguous genitalia is done by External Masculinization score (EMS) ranging from 0-12 and a score less than seven is considered as genital ambiguity. (Ahmed, 2000)
7. **Degree of virilization of an apparent female is determined by prader scale.** This scale consists of five stages ranging from stage 1, a phenotypic female with mild cliteromegaly to stage 5, a phenotypic male with hypospadias.

5. Results

Socio-demographic characteristics of study participants

This study involved a total of 54 patients, which were evaluated at the endocrine OPD in the study period. Age at first presentation ranged from 1 day to 15 years, with mean age of 2.2 years and median of 5.5 months. In this study majority of patients (44.4%) were from the neonatal age group.

All the patients that presented to seek medical attention in the neonatal age were delivered at Health facility. Although the family income couldn't be assessed in majority (38.9%) of patients, 37% of the patients came from Low-income family, 4 % from lower middle class family and the remaining 16.7 % came from upper middle class family. The socioeconomic status of the patients' families was assessed with World Bank Data for Ethiopia, 2015 [Table 1].

Table 1: Socio demographic characteristics of DSD patients on follow up at Endocrinology unit (n=54)

Variables		Frequency	Percent
Gender of Rearing			
	Male	39	72.2
	Female	15	27.8
Age on Presentation			
	0-28 days	22	40.7
	29 days -12 months	6	11.1
	13-47 months	8	14.8
	2-5 years	9	16.7
	6-11years	7	13
	12-18 years	2	3.7
Educational level of Mother			
	Illiterate	6	11.1
	primary,middle school	13	24.1
	Highschool,diploma	10	18.5
	Graduate, Postgraduate	6	11.1
	Not known	19	35.1
Educational level of Father			
	Illiterate	4	7.4
	primary,middle school	14	25.9
	Highschool,diploma	8	14.8
	Graduate, Postgraduate	11	20
	Not known	17	31.5
Place of Residency			
	Urban	42	77.8
	Rural	8	14.8
	Undocumented	4	7.4

Patient	Explanation of circumstance of fetal/neonatal loss	Presumed diagnosis of the patient on follow up
1	1 Still birth, 1 neonatal death after repeated vomiting episodes and weight loss	Salt wasting CAH
2	Early neonatal death which is not explained	Salt wasting CAH
3	1 Still birth	Turner syndrome
4	1 neonatal death, neonate had cleft palate and cleft lip and had difficulty feeding	Presumed XY
5	1 neonatal death which is not explained	Presumed XY
6	The twin of the patient died at neonatal age, due to asphyxia	Presumed XY

Parental Consanguinity

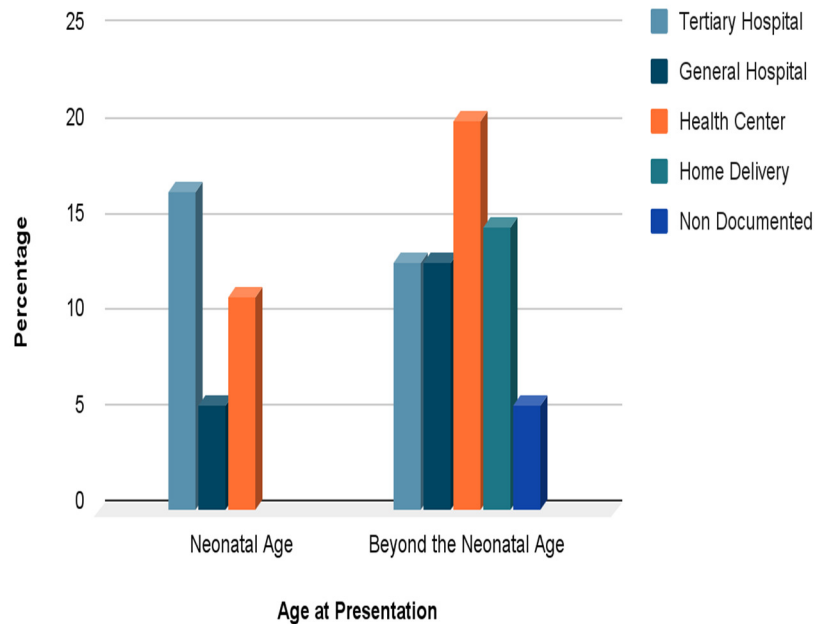
Of the 54 patients, 44 (81.5%) had no history of parental consanguinity, whereas 8 (14.8%) had no documentation. 2(3.7%) of the 54 patients had history of parental consanguinity, where both patients had third degree parental consanguinity. The parents of both patients were first Cousins. One of these patients was diagnosed with CAH at the age of 2 years and later died. The parents were cousins and have another female child who is not screened but is asymptomatic. The other patient who is born in to a consanguineous marriage is presumed to have XY DSD.

Antenatal drug exposure

Majority of the patients (74%) had no history of antenatal drug exposure, while three patients (5.5%) had antenatal drug exposure. The rest 11(20%) had no documentation of antenatal drug exposure. Two mothers had a history of use of progesterone in the first trimester for IVF while one mother had a history of heparin usage. One of the patients whose mother took progesterone had no karyotype done but presumed to have 46 XY DSD. The second patient has a 46 XY DSD, with specific AR exon deletion and copy number changes on NR5A1.

Place of delivery: Majority of patients (24.6 %) were delivered at a general hospital. All patients did not have any prenatal diagnosis. Compared to home deliveries, majority delivered at tertiary hospital presented at neonatal age(P-value – 0.01)

Age at Presentation with Place of Delivery



Initial Presenting symptoms

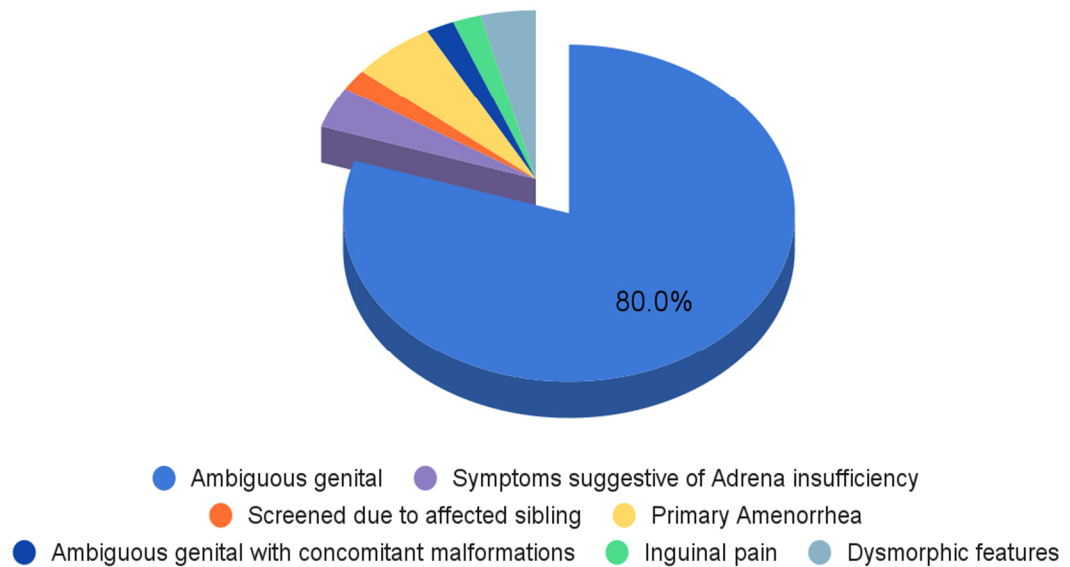
Majority (80%) of the patients presented with observation of ambiguous genital. Additional 5.6% (3) had ambiguous genital along with congenital malformations. The following are the reasons that made the family or the health professional seek medical attention.

Table3; Frequency of complaints at presentation

Complaints at presentation	Frequency	Percent
Ambiguous genital	43	79.6
Symptoms suggestive of Adrenal insufficiency	2	3.7
Screened due to affected sibling	1	1.9
Primary Amenorrhea	1	1.9
Ambiguous genital with concomitant malformations	3	5.6
Referred after diagnosis was settled	1	1.9
Inguinal Pain	1	1.9
Dysmorphic features	2	3.7

Patients with ambiguous genital were more likely to present at an earlier age having a P Value of 0.018 when correlation was done.

Complaints at Presentation



10 patients had syndromic features/ multiple congenital malformations. There were 4 Down syndrome Patients , from whom one presented after family noticed Speech delay , the other 2 were brought for noticing ambiguous genital (hypospadias and undescended testes)

No	Evaluation on presentation	Syndrome considered	Presumed diagnosis of DSD
1	Lower body hemangioma, Club foot and ambiguous genital	LUMBAR syndrome	CAH
2	High arched palate, micrognathia, low set ears, polydactyl, hypospadia and undescended testes		
3	Hypospadia, club foot, micrognathia, high arched palate		
4	Bilateral leg edema, low set ears, Broad chest with widely spaced nipples, low hair lines, webbed neck	Turner Syndrome	Turner Syndrome
5	low set ears, Broad chest with widely spaced nipples, low hair lines, webbed neck	Turner syndrome	Turner syndrome
6	Short stature, Lt mal rotated and Rt ectopic pelvic kidney		46 XX(defect on NROB1)

Anthropometry:

WHO growth standard curves were used to assess the anthropometry of the patients that presented out of the neonatal age. Majority of the patients that is 24 patients had normal height for age, 6 patients with moderate stunting, 3 with severe stunting and 1 patients had tall stature. The patient with tall stature is a Non classic 21-hydroxylase deficiency CAH patient. Two of the three patients who had severe stunting were tuner syndrome patients.

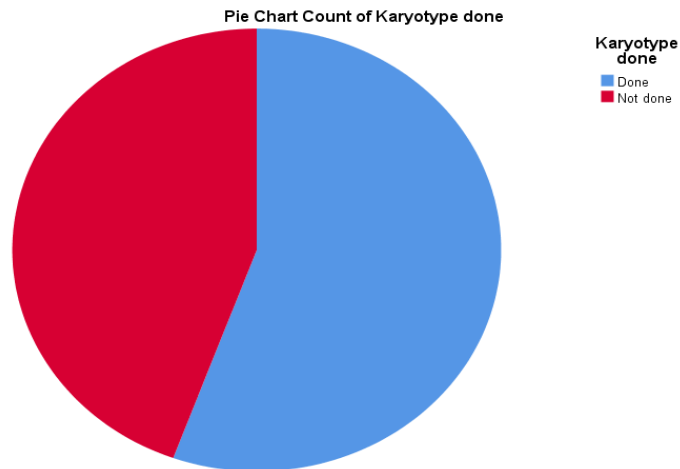
Out of 22 patients, 13 patients showed Normal birth weight, 7 had LBW, 1 VLBW and one had unknown birth weight. Weight for gestation age was recorded for these twenty one neonates, thirteen of them had AGA, seven with SGA.

Blood Pressure

Majority of patients (76%) had no measured blood pressure. 10(18.5%) had normal blood pressure, 2 (3.7%) hypertensive, and 1 (1.9%) had hypotensive blood pressure measurement. One of the patients who had hypertensive Blood pressures on presentation was a 2 years old salt wasting CAH patient who was on medication (Fludrocortisone and Hydrocortisone) at a referring hospital prior to first presentation to this hospital. The blood pressure was believed to be a medication complication. The patient who was hypotensive on presentation is a 6 years old CAH patient who was initially in shock and required admission to ICU. Adrenal Insufficiency was considered to be the cause of the low Blood pressure records which subsequently improved.

Presumed Diagnosis

The lack of hormonal tests, our inconsistent use of molecular genetic analysis, and other investigations have made the etiological classification of DSD difficult. Since most of our patients couldn't afford genetic testing, Karyotype was done only for 30 (55%) of the patients enrolled in the study. Therefore in such a resource limited set up, we had to mainly rely on clinical, ultrasound, and for those who could afford genetic tests and hormonal analyses for classification of the DSD. It was on the basis of this that operational definitions for presumptive categorization were defined.



Karyotype Confirmed diagnosis		
Main Etiologic Classification	Frequency	Percent
46 XX DSD	6	20
46 XY DSD	21	70
Sex chromosomal DSD	3	10

For the purpose of better description and analysis, physical findings, investigations and managements are categorized according to the presumed diagnosis given, which included 46XX DSD, 46 XY DSD and sex chromosomal DSD

46 XX DSD

- Out of 11 patients with presumed 46 XX DSD, 10 (18.5%) have CAH.
- In our study Majority 4 (40%) of the CAH patients presented in the neonatal age. All the 4 CAH patients who presented in the neonatal were delivered in Health facility, with 3 being delivered in a Health Center and one was delivered at a General hospital. All the 3 Patients that were delivered in Health center were referred due to ambiguous genital detection. And two of them were referred on the first day of life, while the other one was referred at 15 days of life after family took her to HC observing hemangioma and club foot, where genital ambiguity was peaked. The 2(20%) of patients presented in infancy, with one referred from

Hospital for genital ambiguity while the other was called for evaluation at 3 months of life for family screening. This patient was delivered in a private General Hospital setup but genital ambiguity was not detected.

Age at Presentation of the Subtypes of 21-hydroxylase deficiency CAH patients

		salt wasting	Simple virilizing	Non classic	Percentage
Age at Presentation	0-28 days	4	2	0	60
	2-5 years	1	2	0	30
	6-11 years	0	0	1	10

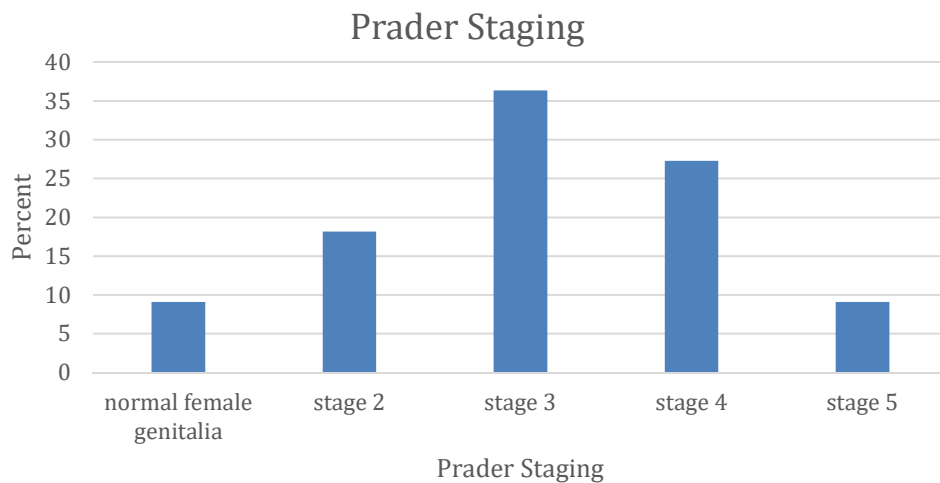
- Three (30%) CAH patients visited our hospital in the age category 2-5 years. One was delivered at home in to a consanguineous, the other patient was delivered in a Hospital. Third patient from this group was referred from BLH for continuation of follow up but was diagnosed at 30 days of life. The patient who presented at 6 years was delivered at a private general hospital and was noted to have signs of precocious puberty and highly virilized. She was diagnosed with Non classic 21-hydroxylase deficiency CAH.
- The 10 CAH Patients presented had variable degree of virilization of the external genitalia on initial examination. Majority 4 (40%) of the CAH patients had Prader stage 3 on evaluation. Two (20%) of the patients had simple virilization degree with Prader stage of 2. The remaining 4 had high degree of virilization, evidenced by prader stage 4 in 3 (30%) and 1 (10%) had Prader stage 5. The patient who had prader stage 4 was reared by the family as male.
- 60 % (6) of the CAH patients had hyperpigmentation of the genital documented while no documentation was found for 3(30 %) of the patients.
- Clitoral/Phallic length of the patients ranged from 2 cm up to 4 cm, with the mean Phallic length of 2.72cm.
- Two patients had precocious puberty on evaluation evidenced by pubic hair SMR of stage 3 each at the age of three and six years. One of these patients presented to our emergency at the age of 6 years with repeated vomiting episodes and was admitted to ICU with signs of adrenal insufficiency suggested by shock and

Hypoglycemia. After her admission to ICU she was noted to have signs of Precocious puberty evidenced by Pubic hair SMR stage 3 which was the entry point to examine and investigate. She was found to be highly virilized, subsequently She was investigated with 17-OHP- of 33.85ng/dl and karyotype with genetic testing showed 46XX , with mutation noted on Exon 4 I172 N of CYP21A2, suggesting simple virilizing CAH. Her sibling was later diagnosed earlier at the age of 3 months during sibling screening.

Table. Revised genital examination findings of presumed CAH patients

Genital Examination Findings		Frequency	Percentage
Pigmentation	Normal	1	10
	Hyperpigmentation	5	50
	Undocumented	3	30
Prader staging	Stage 2	2	20
	Stage 3	4	40
	Stage 4	3	30
	Stage 5	1	10
Clitoral length	2.00	2	20
	2.5	1	10
	3.00	3	30
	3.70	1	10
	4.00	2	20

Patients with higher prader stage were more likely to present at an earlier stage indicated by a P-value of 0.04



Half of the 10 patients who were presumed to have CAH had a karyotype and genetic test; the other half were assigned a diagnosis clinically based on their 17-OHP level and the operational definition. The discovery of a mutation in the CYP21A2 gene provided confirmatory diagnosis for the five patients with the genetic test. On one patient in addition to the genetic alteration on CYP21A2 gene, decreased copy number of NR5A1 gene was seen. This patient had a low cortisol level as well. Serum electrolyte determination was normal. She had a baseline 17OHP of >54 ng/ml and the patient later died and her case will be discussed below under the title of current status of the patients.

17-OHP level was done for all the patients except one who couldn't afford the test to be done. The result of the other 9 patients ranged from 19.25ng/ml to 487ng/ml. Cortisol was not done for 5 of the CAH patients, while 4 had normal baseline cortisol levels. Out of the 10 (18.5%) presumed CAH patients, 5 had the salt wasting 21-hydroxylase deficiency form, 4 had the simple virilizing 21-hydroxylase form and 1 patient was diagnosed with the Non classic 21-hydroxylase deficiency CAH type. The clinical profile of the four Simple virilizing 21-hydroxylase deficiency CAH patient has been presented elsewhere in the study. 4 out of the 5 Salt wasting 21-hydroxylase deficiency patients presented at the neonatal age and one presented at the age of 5 days. The reason for seeking medical attention was Ambiguous genital in 3 of them and only 2 sought medical attention for symptoms suggestive of adrenal insufficiency. The clinical Profile and

management of the 5 Salt wasting 21- hydroxylase deficiency CAH has been summarized in the following table.

.	Age at presentation	Referred from	Reason for evaluation	Physical Findings	Investigation	Management
1	1 st day of life	Health center	Ambiguous genital	Prader stage 4 Hyperpigmented genital	Hyperkalemia/Hyponatremia 17-OHP- 326ng/ml Genetic mutation on CYP21A2 RBS- Normal	Hydrocortisone Table salt Fludrocortisone
2	7 th day of life	General Hospital	Vomiting and Failure to thrive	Prader stage 3 Hyperpigmented genital	Hyperkalemia/Hyponatremia 17-OHP- 37ng/ml Genetic mutation on CYP21A2 RBS- Normal	Hydrocortisone Table salt Fludrocortisone
3	30 days Referred to this hospital at 2 years		Vomiting, diarrhea and Failure to thrive			Hydrocortisone Fludrocortisone
4	1 st day of life	Health Center	Ambiguous genital	Prader stage 4 Hyperpigmented genital	Hyperkalemia/Hyponatremia 17-OHP- 487ng/ml RBS- Normal	Predinsolone Table salt Fludrocortisone
5	35 days	General Hospital	Ambiguous genital	Prader stage 4	Hyperkalemia/Hyponatremia	Predinsolone Table salt Fludrocortisone

In our study, the only patient in 46 XX DSD category, that doesn't have CAH is presumed to have a defect in Ovarian development due to the NROB1 anomaly. She is our only patient who presented with primary amenorrhea. She also had short stature. She had investigation results of high FSH and LH , and Low estradiol. Abdominal ultrasound showed small uterus, ectopic kidney and contralateral malrotated kidney. She was initiated on OCP and her menses started but later was lost from follow up.

Medical Management summary of Presumed 46XX DSD patients			
		Frequency	Percent
Medical Management	Hydrocortisone	1	9
	Prednisolone	3	27
	Hydrocortisone, Fludrocortisone and table salt	4	36.4
	Fludrocortisone and Hydrocortisone	1	9
	On Hydrocortisone and Leuprolide	1	9
	OCP	1	9

Cushinoid features were documented as a complication in 2 of the patients who were on Hydrocortisone, Fludrocortisone and hypertension was identified on one patient on Hydrocortisone and Fludrocortisone. Of the three patients for which bone-age were done, 2 patients had advanced bone age, while the other one patient bone age is appropriate

46XY DSD

Out of the 54 patients enrolled in our study, 38 are Presumed to have 46 XY DSD according to the operational definition set. Karyotype and specific genetic tests were done for 21 patients (55%) out of the 38 Presumed 46 XY DSD. Total number of karyotypes done in this study was 30, meaning 70% of the karyotype done was for presumed 46 XY DSD patients. 35 (92%) of the presumed 46 XY DSD patients presented with ambiguous genital. While two (5.3%) had ambiguous genital with

concomitant congenital malformation. Only 1 patient presented to seek health care after complaining of inguinal pain.

The patients presented with variable degree of genital ambiguity assessed based on EMS.

- Majority that is 28 (74%) of the patients had microphallus, while 9(24%) of patients had normal penile length for age.
- Gonadal examination showed bilateral inguinal palpable gonad for the majority (42%) of patients

Table – Site of palpable gonads on Examination

Palpable Gonads	Frequency	Percent
Bilateral, inguinal	16	42
Bilateral Labioscrotal fold	11	29
Unilateral, inguinal, other not palpable	1	2.6
Unilateral Inguinal other scrotal	3	7.9
Unilateral scrotal, other not palpable	2	5.3
Not palpable	3	7.9

Investigation

- Cortisol was done for 19 (50%) of the presumed 46XY DSD patients. It was normal for 17(45%) and low for 2 (5%) of the patients. The two patients with low baseline cortisol levels have normal electrolyte parameters and karyotype with specific genetic mutations was done which didn't reveal significant copy number change for screened genetic mutations. Repeat cortisol levels were subsequently in the normal range.
- Serum ACTH was not consistently available and thus was not done for majority (82%) of the patients. ACTH was normal in 6 (16%) of the patients.
- Ultrasound was performed for all patients. Ultrasound findings showed inguinal testes location for 20 (53%)patients

Ultrasound finding	Frequency
Inguinal testes	20
Abdominal Testes	2
Inguinal testes/abdominal testes	2
Bilateral scrotal	12
Rt inguinal testes/Left ectopic kidney	1
Bilateral Inguinal testes and solitary kidney	1

No.	Genital Exam	Imaging	Other Pertinent Results	Genetic mutations identified	Possible Mutation and Etiologic Diagnosis
12	Microphalus,bilateral palpable inguinal gonads, Bifid scrotum, Penoscrotal Hypospadia with chordee Birth weight was 2.47kg , length was 48cm Has no skeletal deformities External masculinization score of 2	Inguinal testes bilateral	Serum cortisol and ACTH was not done RBS-Normal	Has 2 karyotypes done 1. The sex reversal gene DAX shows significant copy no change 2. The NR5A1 gene, exon 1-4 shows signifant copy number change (decrease), exon 1 of SOX9 and AR also shows decreament WNT4 gene is deleted	Mutations on NR5A1, AR and SOX9 can explain scenario
1	Microphalus, bilateral palpable inguinal gonads, External masculinization score of 2	Inguinal testes bilateral	Cortisol/ACTH-Normal	Copy number change on NR5A1 and exon 1 of WNT4	NR5A1 mutation
14	Microphalus, bilateral palpable inguinal gonads, External masculinization score of 2	Inguinal testes bilateral		Significant copy number changes (deletions) was observed on genes (CDY1B,BPY2 and DAZ2 on Yq11.23) Microdeletions/duplications in the AZF sub-regions a,b, or c	Yq11.23 mutation
17	Normal penile size, bilateral descended testes in scrotum External masculinization score of 7	scrotal		Significant genetic alteration on SOX9 and WNT4	Both can explain the scenario
38	Microphalus, bilateral palpable inguinal gonads, External masculinization score of 4	Inguinal testes bilateral		Significant copy number changes are observed on genes located on RBMY1J, BPY2 and DAZ2 of Yq11.23	Yq11.23 mutation
30	Normal penile size, bilateral descended testes in scrotum External masculinization score of 6 Had club foot+ Patient later died	scrotal	Cortisol/ACTH was not done Potassium was high Sodium was normal RBS-Normal	Ambiguous copy number change of dosage sensitive DAX gene	Mutation on DAX1 gene

19	Microphalus , bilateral descended test in labioscrotal area, Bifid scrotum and penoscrotal Hypospadia External masculinization score is 3			Exon of 5 alfa reductase and CYP17A1 gene shows ambiguous copy number change	
22	Penile length is normal, Bifid scrotum , palpable testes in scrotum and penoscrotal hypospadia EMS is 6 No skeletal deformities		Normal Cortisol	The DMRT1 gene exon shows ambiguous copy no change (decrease) Exon 4 of the AR gene shows significant copy number change(decrease) SOX9 also shows decreased copy number and exon 1 of the WNT4 appear deleted	
20	Microphalus, unilateral inguinal palpable testes (other side detected by ultrasound in the upper inguinal canal) EMS-3			Some exons of the NR5A1 gene show decreased copy number. Exon 1 of the AR gene shows significant copy number change (decrease)	AR mutation
32	Unilateral inguinal other side scrotal testes EMS-3.5	Unilateral undescended inguinal		Deletion observed on Yq11.23 Deletion was observed on PPP1R12BP and RBMY2DP of Yq11.23	Yq11.23 mutation

For those that had karyotype done (55%), Specific genetic mutations were assessed. And out of the 21 patients that had karyotype done 11 (52.4%) of the karyotyped patients had a result showing no significant copy number change for screened mutations. The result of the 10 (48%) of the karyotyped patients will be summarized in the following table with pertinent clinical profiles and investigations needed to interpret the genetic mutations detected.

Specific Genetic Mutation confirmed

	Percentage of the 46 XY DSD
Androgen Insensitivity Syndrome	5.2%
XY Gonadal dysgenesis	18%
5-alpha reductase deficiency	5.2%

10 patients were found to have undergone surgical management, of which 4 (40% of those who underwent surgery) underwent urethroplasty.

Surgical intervention	Frequency	Percentage
Urethroplasty	4	40
Orchidopexy	1	10
Orchidopexy and urethroplasty	2	20
Urethroplasty and chordea release	1	10
Urethroplasty and peno-scrotal transposition correction	2	20

SEX CHROMOSOMAL DSD

Three (5.5%) patients have been categorized under this category. Two of the patients have Turner Syndrome of which one has karyotype and the other was diagnosed clinically because of financial issue. One of the patients was brought at the age of 45 days after mother noticed bilateral leg swelling. She had dysmorphic features and had a karyotype proven diagnosis. Patient is currently on Growth hormone. The other Turner syndrome patient presented at the first day of life (St. Paul delivery) after noted to have dysmorphic features and respiratory distress. Both patients have normal echocardiography result. The other patient in this category is a klinefelter syndrome

patient who was evaluated after he presented with a complaint of small penile size at the age of 12 years. Karyotype showed 47XXY.

Presumed ovotesticular DSD

Presumptive Classification of two patients was presumed to be Ovotesticular. The first is a patient who presented at the neonatal age and has unilaterally palpable gonad, Bifid scrotum, stretched penile length of 2 cm and a single urogenital opening, Imaging showed that uterus is identified , with Left undescended testes and Right was difficult to visualize with ovaries not visualized. Patient was lost from follow up before further investigation was done.

The other patient presented at the age of 10 months for ambiguous genital. Physical findings showed Bifid scrotum with no palpable gonads, Penoscrotal hypospadias with chordee. Exploration and Biopsy showed Rt fallopian tube +Lt testicular tissue Uterus with cervix was visualized with no vagina (agenesis). Karyotype showed 47XXY with Significant copy number changes on NROB1, Cxorf21 and GJB1 genes. Labiaplasty + Clitoroplasty + Ectopic testes removal was done and gender of rearing was changed from male to female.

Gender assignment

Gender Re-assignment	Frequency	Percent
Was not changed from gender of rearing	46	85
Counseled and family didn't decide	3	5.5
Was changed	3	5.5
Not discussed	2	3.7

Gender of Rearing and clinically and karyotypically assigned Sex were the same in 85% of the patients. From the two patients on whom Gender assignment was not discussed

was one was karyotypically proven 46 XY DSD with ambiguous copy number change on Exon of 5 alfa reductase and CYP17A1 gene. Gender of rearing for this patient was female and currently the patient is lost from follow up. The other patient on whom gender assignment counselling was not discussed with MDT and family was a patient who had been lost from follow up. This is the patient discussed above under the category of difficult to classify. Patient presented at the neonatal age with gender of rearing of male was lost from follow up with out further investigation and gender role discussion.

The patient for whom gender re assignment was done after discussion with family and MDT is the patient discussed above with karyotype of 47 XYY, for whom cliteroplasty, labioplasty and ectopic testes removal was done. The patient's gender of rearing has changed from male to female.

Follow up status

Regarding current follow up status of patients, 29.3% of patients are on follow up at endocrine clinic.

Follow up status	
On follow up at endocrine clinic	14(25.9%)
On follow up at endocrine and surgical clinic	9(16.7%)
On follow up at surgical side	5(9.3%)
Lost from follow up	10(18.5%)
Waiting on admission for surgery	13(24.1%)
Dead	3(5.6%)

Patients who died

Three patients have died while on follow up. Patient was on follow up with the assessment of CAH at the age of 2 years after she presented with ambiguous genitalia and was born in to a consanguineous marriage. Delivery was at home. Karyotype was not done and 17-OHP was 19.2 ng/ml. Patient was on prednisolone for 5 months. Patient died at a nearby health center after a complaint of repeated episodes of diarrhea and vomiting of 1 day duration.

The second patient was also on follow up with the assessment of CAH after she presented with ambiguous genital at the age of 2 years. Karyotype was done indicating 46 XX chromosome and genetic alteration on CYP21A2 gene was noted. Baseline 17OHP was > 54ng/ml. Patient was on Prednisolone. The last 17OHP determined for follow up was 44ng/ml. Patient died at a near by hospital after a complaint of excessive fatigue and weakness as the family described and died at the age of 3 years.

The third patient who died was delivered at the St. Paul Hospital and referred for evaluation of Club foot+ respiratory distress and ambiguous genital on the same day of birth. He was delivered as a Term(37weeks) +LBW(1.9kg)+SGA(S). Patient had microphalus, penoscrotal Hypospadias palpable gonads in the labioscrotal fold. Serum cortisol and ACTH was not determined. Serum potassium level was high (6.38-7.4). Karyotype showed 46 XY and Ambiguous copy number changes of dosage sensitive DAX gene was noted. Possible cause of death of all the three patients can be explained by Adrenal insufficiency.

6. Discussion

There are limited published data on DSD in Africa, specially in Sub-Saharan countries. (Kihiko, 2016) Similarly the prevalence of DSD in the Ethiopian population is unknown because, to our knowledge, there have been no publications of data on this topic. Data on the classification and clinical characteristics of DSD patients will be made available for the first time in the nation by our study.

Most African countries have a higher percentage of home births, and DSD is stigmatized in many communities, which causes patients to seek medical attention late. (Kihiko, 2016; Shamma, 2021) Despite this , In our study the majority of patients presented in the neonatal period(40%). This in contrary to a study done in Egypt where majority(60%) of the patients presented after the age of 1 year. (Shamma, 2021)

The reason why the majority of our patients presented with in the the first year of life with a median of 5 months is probably because most of our patients (around 30 percent) are delivered in a tertiary hospital setup , where better trained professionals including neonatologists and endocrinologists are available. But we still believe that this number might not be representative and that there are still a significant number of patients missed and not getting the medical care they deserve.

Our data revealed that the most common presumed causes of DSD in our study were 46 XY DSD (70%), with 46XX DSD in second place (20%) and lastly sex chromosomal DSD . This was in concordant with results from other African countries; In a study published in Egypt and south Africa it was shown that 46 XY was the most prevalent etiologic diagnosis, representing 65.9 % and 57.5% of the cases respectively. (Shamma, 2021; Yasmeeen Ganie*, 2016) . Likewise there are literatures done outside of Africa supporting the dominance of 46XY DSD; In turkey 47% of the 95 DSD (Sema Erdogan, 2011) patients and 48.7% of the 39 DSD patients in a tertiary hospital in India had 46 XY (Jahagirdar Rahul, 2020). On the contrary in a case series done in Saudi Arabia it was observed that 53(65.4%) were 46 XX and 28(34.6%) had 46 XY DSD. (NAM, 2010)

According to Lawson Wilkins Pediatric Society, 46 XY DSD can be roughly categorized into three groups with further subcategories, as 1. Disorder of Testicular development 2. Disorders of Androgen Synthesis or action and 3. Others. In developed countries advanced molecular and genetic studies, testicular function assessment by using the hcg stimulation test and other hormonal assays and other investigations are carried out to classify 46 XY DSD patients in to the broader categories and further. Even in these situations, the likelihood of obtaining a molecular diagnosis of 46 XY despite conducting clinical and biochemical testing is low. (Audi, 2018)

In a setup with few resources like ours, we lack access to such investigations. Thus, of the 38 assumed 46 XY DSD individuals, only 55% (21) had a karyotype performed. And none of the patients had hcg stimulation test done. We emphasize that one of the major limitations in reaching a definitive diagnosis among the patients in 46 XY DSD in our study is the unavailability of hormonal analysis and the inconsistent use of molecular genetic analysis in our center. For this reason, we defined 46 XY DSD based on the operational criteria previously established, and from there we attempted to further make an etiological diagnosis based on the presence or absence of evidences of adrenal insufficiency and genetic mutations detected. Such etiological classification attempt of the 46 XY DSD patients was done only in those patients who had karyotype and specific genetic testing done. Thus further etiologic diagnosis was not attempted in 45% (17) of the Presumed 46 XY DSD patients.

The genetic mutation attributed to be the cause of genital ambiguity of one our patients who had copy number changes (decrease) on NR5A1 and exon 1 of WNT4 was believed to be the copy number decrement of NR5A1. This patient first presented at the age of 2 years and 3 months with a complaint of genital ambiguity. Genital examination showed Bilateral inguinal palpable gonad, Microphalus (2.3 cm), bifid scrotum and penoscrotal hypospadias. RBS, Serum cortisol and ACTH was done and was in the normal range. In this patient the NR5A1 gene mutation was incriminated as the explanation of the patient's condition because had it been the WNT4 mutation its duplication would have

described the patient's clinical scenario rather than its decrement. WNT4 regulates ovarian development so in 46XY patients its duplication can cause testicular regression.

The second patient presented at the first day of life for evaluation of ambiguous genital, after delivered in our hospital. He had normal penile length, bifid scrotum, bilaterally palpable gonads in the inguinal region and penile hypospadias. Patient had no skeletal deformities. Serum electrolyte and RBS was in the normal range but serum cortisol and ACTH was not done. Significant genetic alteration on SOX9 and WNT4 was noted on this patient. Although the patient doesn't have skeletal deformities both mutations can be attributed for the patient's clinical condition.

The third patient we had significant copy number change (decrement) on NR5A1 gene and SOX9 and AR also showed decreased copy number changes. WNT4 gene deletion was also noted on this patient. This Patient presented on first day of life with ambiguous genital and the EMS score was 2. The Cortisol and ACTH levels were not determined in this patient. He also doesn't have Skeletal deformities which could have supported the SOX9 mutation to be the explanation for the clinical scenario. As stated, HCG stimulations test was not performed which would have supported against or for Androgen insensitivity. So in this patient we have difficulty in attributing the clinical scenario to a specific genetic mutation.

Significant copy number changes and deletions of yq11.23 was noted in 3 patients who presented with genital ambiguity of EMS score of 2 -4. In general structural abnormalities of the Y chromosome are estimated to affect less than 1 % of new born male population (kim, 2012). We found 2 case reports on pediatric age patients. In both patients from the two case reports the patients had concomitant other chromosomal abnormalities. The first Patient who is a 15 years old syndromic patient, had duplication of 17p11.2p12 along side the Yq11 deletion. The AZF region necessary to promote and maintain spermatogenesis was affected in this patient. (Liliana, 2019) The other case report we found was on a 4 years old who is diagnosed to have Williams - Beuren Syndrome. The patient had deletion of

Yq11.23 along 7q11.23 deletion. The patient had dysmorphic facial features such as full orbital, spherical nose, thick lips , wide mouth and irregular teeth. (Liu-Xu, 2021) But unlike these patients all 3 of our patients with this mutation had no dysmorphic features.

Globally CAH, which results from 21-hydroxylase enzyme deficiency, is the most common cause of genital ambiguity in newborns, occurring in around 1 in every 15,000 live births. (Speiser, 2001). Even while in our study 91% (10) of the 11 Patients presumed to have 46 XX DSD were found to have CAH, the figure is modest when seen from the perspective of the entire study group, accounting for just 18.5% of the study population. Other literatures done in other African countries have similarly shown a lower incidence of CAH than would be predicted based on global data. A study done in Nigerian hospital in 2018 has found similar figure with only 20%(3) of their study population of 15 patients were diagnosed with CAH. (Nasir, 2018) The study population they used in this population was only 15 which makes it even lower than our study population. In another study done in Kenya in 2019 on 71 patients CAH was the second most common cause of DSD second to ovotesticular DSD . A study conducted in Egypt that found CAH to be the most frequent etiological diagnosis within the 46XX DSD group (90.5%) but the second most frequent cause of DSD overall (21%) supports our study. (Shamma, 2021) On the contrary in a study done in Kenyatta Hospital 46 XX DSD was the most (43%) prevalent cause of DSD. (Kihiko, 2016)

Although as discussed above, since definitive etiologic diagnosis of the 46 XY DSD patients was not possible it is difficult to compare frequency of etiologic diagnoses. But the lower-than-expected figure of CAH in our study could be due to mortality of missed patients with salt wasting CAH. Due to the fatal adrenal insufficiency in this group, professionals with awareness on the area are needed to identify these patients early. The fact that 20%(2) of the 10 CAH patients enrolled in the study has family history of neonatal losses before diagnosis was settled favors this assumption. Only 40 Percent of the CAH patients were referred for evaluation at the neonatal age after genital ambiguity was noted at referring Health centers, which is plausible. But we still believe that there is

gap in awareness of health professionals in having a proper genital examination for every new born. In such a resource limited setup like ours where neonatal screening for CAH is not implemented, health professionals should rely on their high index of suspicion and clinical findings.

The third frequent DSD group in our study was chromosomal DSD(5.5%). Similar figures were noted in studies done in Egypt and Kenya with chromosomal DSD attributing to 5 % of the study population. (Shamma, 2021) (Prisca Amolo, 2019). On the contrary a study done in Turkey in 2011 it was noticed that 27%(26) had Chromosomal DSD with Turner syndrome accounting to 80% (20) of the chromosomal DSD

The least frequent group was Ovotesticular DSD accounting for 3.7% of the study population. On the contrary in a study done in Kenya the most common cause of DSD identified was ovotesticular DSD (14.1 %) (Prisca Amolo, 2019).

Limitation of study

Further classification and specific etiologic diagnosis was not possible due to unavailability of HCG stimulation test and molecular genetic tests. In addition to this cortisol and ACTH was not done in majority of patients, which made classification more difficult. As this is a retrospective descriptive study the usual issues of data integrity like missing data accompany it. These issues may have resulted in bias in our observation and the data does not represent prevalence of disease in our population.

7. Conclusion and recommendations

7.1. Conclusions

Result showed that there is delayed presentation of patients. Ambiguous genital is the most common presenting complaint. Majority of Patients have 46XY DSD. It also inferred that CAH is under diagnosed.

7.2. Recommendations

We recommend having intense training of health professionals to perform a thorough genital exam every newborn, and training on detection of adrenal insufficiency. We also recommend to strengthen MDT management as it was seen almost no communication between surgical and pediatrics managing team. It is also noted that some patients are evaluated first at surgical OPD before endocrine clinic, which led to incomplete examination and lost in follow-up, thus we recommend for all DSD patients to be evaluated at endocrine clinic before being transferred to surgical OPD

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