Management of Differences in Sexual Development: Evolution of an Approach for a Resource-Limited Setting

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Abstract

Background: The approach to management of patients with disorders of sex development (DSD) has been refined over the past two decades. We sought to review DSD cases at our hospital and hypothesized that age at presentation would decline over time. **Methods:** A retrospective review of patients presenting to our hospital between January 1, 2005 and July 31, 2018, with findings of ambiguous genitalia was performed. **Results:** A total of 44 patients were identified, 3 with cloacal exstrophy. Of the 41 remaining patients, the majority (n = 24) had ovotesticular DSD. Three time periods in the evolution to a multidisciplinary team (MDT) approach were identified: Period 1 (2003–2009), Period 2 (2010–2013), and Period 3 (2014–present). Median presenting age in Periods 1, 2, and 3 were 7 years (95% CI: 0.5–15), 6.5 years (95% CI: 1–19), and 11 years (95% CI: 2–17), respectively, and were not statistically different. **Conclusion:** Management of patients with DSD poses a challenge to healthcare providers across the globe. The gradual evolution of patient management with incorporation of MDTs and progression toward delayed surgery is seen in this study. There is indeed a need to set up regional centers of excellence, public awareness programs, and healthcare personnel training programs for optimal management of these patients in low- and middle-income countries (LMICs).

Keywords: Disorders of sex development (DSD), Ambiguous genitalia, LMIC, Intersex, Ovotesticular

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Introduction

Disorders of sex development (DSD) represent a complex spectrum of conditions in which there is discordance across genetic, gonadal, and phenotypic sex. These conditions arise when abnormalities occur during the process of sex determination and differentiation (1). Several disorders fall under the umbrella definition of DSD and thus previously used terminology (pseudohermaphroditism, hermaphroditism, sex reversal, etc.) are now avoided (2, 3). The major categories in the current classification of DSD are 46XX DSD, 46XY DSD, and sex chromosome DSD (4).

The global incidence of DSD is estimated to be at 1 in 4500–5000 live births (5). There is a paucity of relevant African literature so that the true incidence in Africa is largely unknown. One study from South Africa reported

a prevalence of 15.1% (6), while studies from Sudan and Egypt have reported prevalence rates of 3.1 and 7.3% (7, 8). There are no published prevalence rates from East Africa. Diagnosis and management are challenging everywhere but particularly in resource-constrained environments. Management strategies have changed over time. We sought to review DSD cases managed at our hospital and hypothesized that age at presentation would decline over time.

Materials and Methods

We performed a retrospective review of all patients who presented to our hospital between January 1, 2005 and July 31, 2018, with clinical findings of ambiguous genitalia and/or a diagnosis of DSD by pathologic testing of gonadal biopsy specimens. The study was approved as an exempted study by the Ethics Committee of our hospital (Aug 31, 2018, P. Halestrap, MD, Chair – Kijabe Hospital IRB).

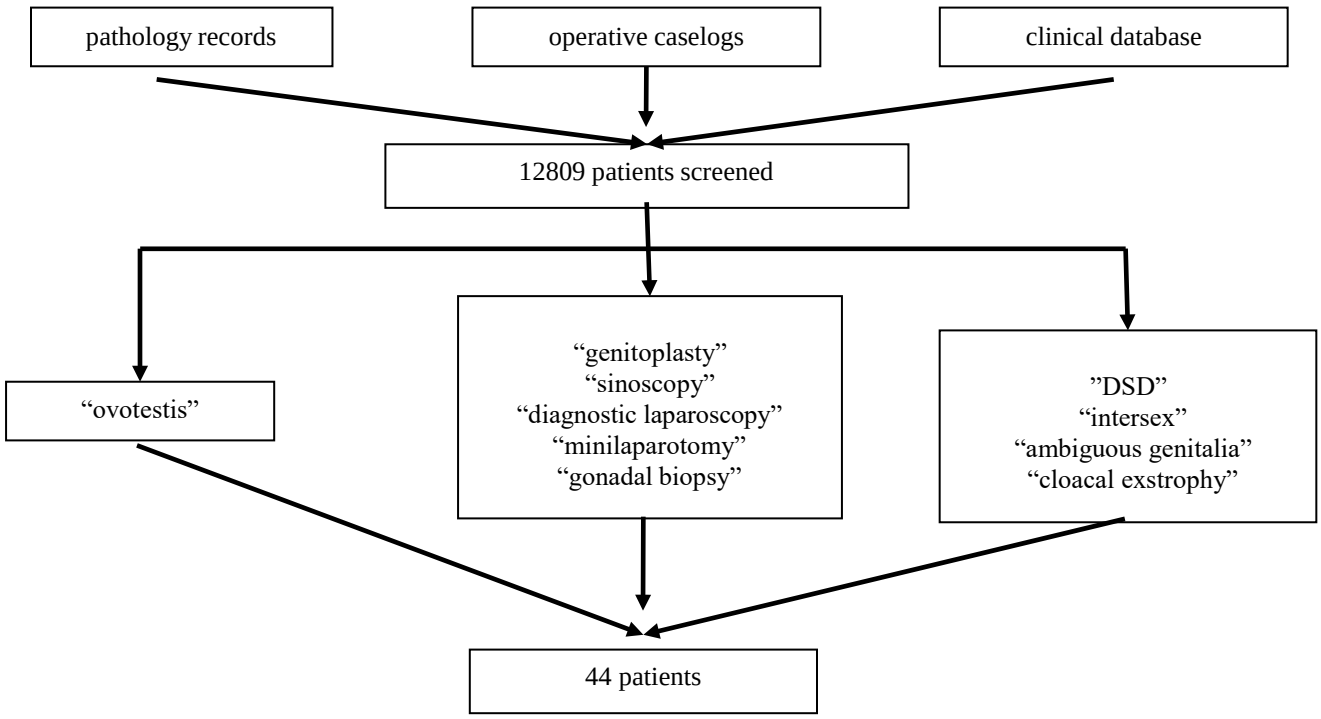

Figure 1 Patient Selection

Data collection

Data were collected from the patient electronic database (Access © 2007 Microsoft), the electronic pathology database (FileMaker Pro, 2019 Claris International Inc. Santa Clara, CA.), and operative case logs. These were searched for ambiguous genitalia, proximal hypospadias, intersex, DSD, gonadal biopsy, and diagnostic sinoscopy to identify patients for inclusion in the study (Figure 1). Diagnostic testing modalities were performed and results were collected. Patients with proximal hypospadias found to have bilateral testes and 46XY karyotype, when testing was available, were excluded.

All patient diagnoses were assigned using the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society nomenclature and classification system (2). Clinical data collected included age at presentation, sex of rearing, family history of consanguinity, presence of Müllerian structures found during diagnostic procedures (laparotomy/laparoscopy/genito-urethroscopy), gonadal

biopsy histology, diagnostic biochemical tests, karyotype, and age at first surgical intervention.

Data analysis

Data were captured in Excel (© 2018 Microsoft) and the Statistical Package for Social Sciences (SPSS, Version 23 © 2015 IBM Corp. Armonk, NY) was used for analyses. Descriptive statistics for categorical data were expressed as counts, percentages, and/or frequencies. Continuous data were expressed as mean and standard deviation or median and range. Nonparametric tests were used to compare ages across time periods.

Results

A total of 44 patients with a diagnosis of DSD were identified.

Table 1. Patient characteristics

CHARACTERISTIC		NUMBER (N = 44) (%)
Gender of rearing		
	Male	30 (68)
	Female	14 (32)
Age (years) at Presentation		
Median		6.5
Birth–1 month		7 (16)
>1 month–1 year		5 (11)
>1 year–<12 years		17 (39)
>12 years		15 (34)
Consanguinity		
Present		3 (7)
Absent		10 (23)
Not recorded		31 (70)
Gonad palpability		
Non-palpable		17
Palpable – unilateral		19
Palpable – bilateral		5
Not recorded		3

Within the study cohort, all patients had an assigned gender at the time of presentation, with 30 patients being raised as male (68%) and 14 as female (32%). Three patients (9%) reported a history of consanguinity. The median age at presentation was 6.5 years (birth–34 years) (Table 1). Three patients had cloacal exstrophy and did not undergo karyotyping or other DSD-specific diagnostic testing. Two of these patients had typical cloacal exstrophy on examination and one patient had an atypical cloacal exstrophy with an intact bladder plate and the hindgut plate attached to the caudal edge of the bladder plate.

Diagnostic modalities

Of the 41 non-cloacal exstrophy patients, one patient had a karyotype and future diagnostic testing planned when older, while 40 patients had one or more diagnostic procedures to evaluate internal genitourinary anatomy: minilaparotomy via Pfannenstiel incision, diagnostic laparoscopy, genitoscopy, and/or gonadal biopsies. Five patients had buccal smears to look for Barr bodies. A total of 21 patients had karyotyping, two of which also had fluorescence *in situ* hybridization (FISH) for SRY gene assay.

Twelve patients had completed a serum hormonal testing (17-OH Progesterone, dehydroepiandrosterone sulfate, androstenedione, testosterone, dihydrotestosterone, 17-beta-estradiol, luteinizing hormone, and/or follicle stimulating hormone).

Table 2. DSD classification

DSD CLASSIFICATION (N = 44)	
Complete androgen Insensitivity syndrome	1
5alpha-reductase deficiency	1
CAIS or 5alpha-reductase deficiency	1
Congenital adrenal hyperplasia	5
Salt-wasting	1
Non-salt-wasting	1
Presumed	3
Ovotesticular DSD	24
46XX	11
46XY/46XX	1
Unknown	12
46XX Testicular DSD	2
46XY/45XO Sex chromosome DSD	1
46XY DSD – Nos	1
46 XX DSD – Nos	1
Cloacal exstrophy	3
Unknown	4

Findings

The DSD classification of patients is shown in Table 2. Of the 24 patients found to have ovotesticular DSD, 12 did not have karyotyping. Congenital adrenal hyperplasia (CAH) was presumed in 3 of 5 patients based on the presentation of ambiguous genitalia, bilateral ovaries, and present Müllerian structures.

Four patients did not have enough diagnostic data to classify. These patients presented between birth and 15 years old with a male gender assignment, and all were found to have Müllerian structures. One had bilateral ovaries; the second had a single ovary, and the third was found to have 10% Barr bodies on buccal smear. The gonadal status of the fourth was unknown.

Three cloacal exstrophy patients underwent hindgut tubularization shortly after birth. In all, 27 patients had reconstructive genital procedures at a median age at first reconstructive operation of 12 years (2–34 years); while a total of 14 patients, with median age of 2 years (0–16) at presentation, were yet to undergo reconstructive procedures.

Evolution of management

The workup of patients with ambiguous genitalia was found to evolve as healthcare resources and trained personnel changed over time. We identified three periods in the evolution of management of patients with DSD at our hospital (Figure 2).

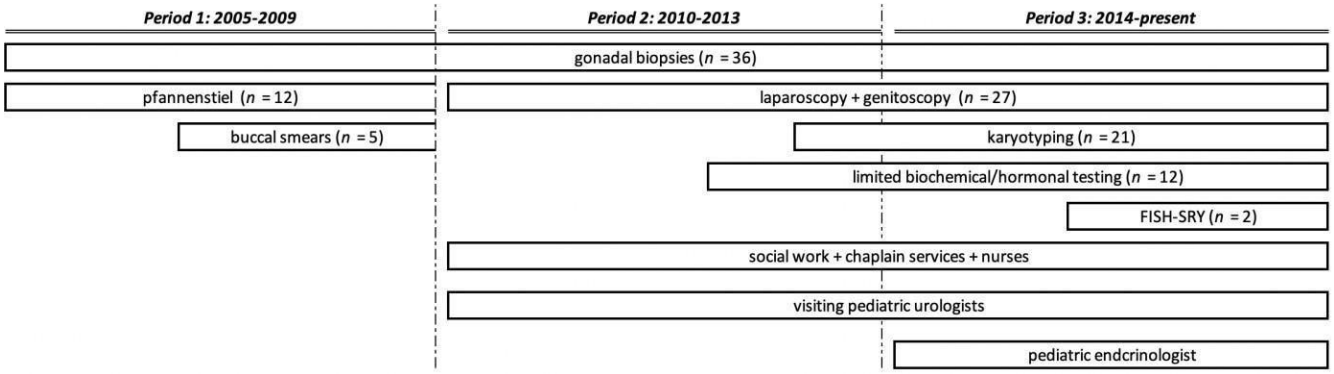

Figure 2. Evolution of DSD management.

Period 1: ~2003–2009

Clinical personnel included a pediatric surgeon with intermittent assistance of a visiting pediatric urologist and/or plastic surgeon. Karyotyping was effectively unavailable. Buccal smears were performed to look for Barr bodies. Gonadal assessment and biopsies were performed via Pfannenstiel incision. Cystourethroscopy was available. The median age at presentation during this period was 7 years (95% CI: 0.5–15).

Period 2: 2010–2013

Laparoscopy was introduced for evaluation of Müllerian structures and gonadal assessment and biopsy. Karyotype, though offered in the country, was still pragmatically unavailable to most of our patients due to the high costs involved. Chaplain and social work services were available. Visiting pediatric urologists assisted with cases as available. The median age at presentation during this period was 6.5 years (95% CI: 1–19).

Period 3: 2014–present

The multidisciplinary (MDT) approach to patient care includes simultaneous evaluation of patients by a pediatric surgeon and pediatric endocrinologist. Karyotyping is more readily accessible through third-party funding mechanisms. The National Health Insurance Fund (NHIF) expanded its services, providing more funding for operative procedures and investigative studies. Social work and chaplaincy are available to help with coordinating funding and to meet with families and patients as a part of discussions about family, personal, and social issues related to their diagnosis. The median age at presentation during this period was 11 years (95% CI: 2–17). The median age of presentation across all periods was not statistically different.

Discussion

Management of patients with DSD poses a challenge to healthcare providers across the globe. Great advances have been made in the past two decades that have refined the approach to management of DSD. However, there is still limited evidence to accurately guide decision-making concerning gender assignment, timing of surgery, and fertility preservation (3). Furthermore, disparities in management between resource-rich and resource-limited settings are glaring. The present study presents a cohort of DSD patients from one institution in East Africa and describes the evolution and development of a pragmatic approach to diagnosis and management within the regional context.

The majority (54%) of our patients were found to have ovotesticular DSD with 11% diagnosed with confirmed or presumed CAH. While reports from high-income countries (9) and text books (10) report CAH as the most common type of DSD, similar rates of CAH and a predominance of ovotesticular DSD have been noted in other centers in Africa, including referral centers in Kenya (6, 11, 12, 13). In a newborn CAH screening program in the United States, the incidence of classic CAH among black Americans was 1:42,000 in contrast to an overall incidence of 1:16,000 (14). These data suggest an underlying genetic difference among patients with African heritage and a likely European and North American epidemiological ethnic bias in the literature published from high-income countries. Our finding of 54% ovotesticular DSD is still higher than that seen in other African literature. This could be the result of a small dataset or referral bias, but our data are insufficient to explain this difference. Khayat (15) and Shawky (8) have reported rates of consanguinity in their respective cohorts of DSD patients of 40% and 55%, respectively, attributable to various religious and cultural practices. In the present study, the rate of consanguinity was at least 7%, as underreporting may have played a role. High rates of consanguinity may affect inheritance patterns and genetic profiling of DSD. In the present study, the median age at presentation was 6.5 years. Other authors have reported similar delays in presentation, some as late as adolescence (16).

Approach to care in the first two periods of study have been previously described (17). The challenges highlighted included late patient presentation, inadequate facilities to make an accurate diagnosis, sociocultural influence of the African community, and loss to follow-up. Similar challenges have been noted in other centers within Sub-Saharan Africa (16). Africa has unique sociocultural influences. African culture [and most low- and middle-income countries (LMICs)] is largely patriarchal and thus the majority of the children born with ambiguous genitalia will be raised as males (18). In one report, more children raised as boys were presented to medical facilities for evaluation of ambiguous genitalia than those raised as girls (5). This bias toward male rearing was also seen in the present study, as 70% of patients with atypical genitalia were raised as males. Additionally, despite the growth of an MDT approach, the median age at presentation of patients did not decrease as hypothesized. This is likely still due to the limited access to care and lack of nationally recognized treatment centers and programs. The median age at reconstruction was also stable across time periods commensurate with the late presentation. Optimal models of DSD Care teams have been described (3, 19). Approach to care in the present study was largely driven by availability of skilled clinical personnel, accessibility of diagnostic tools, and the financial capability of the patients. Progress in the development of a multidisciplinary approach to care over the study period is evident. Emerging subspecialties of pediatric endocrinology, pediatric surgery, and pediatric urology have gradually been incorporated into the patient care team. Involvement of a pediatric endocrinologist has improved patient evaluation and incorporated highly selective targeted testing as a cost saving measure to aid in diagnosis. Furthermore, a team of nurses, chaplains, and social workers now provide contextually appropriate psychosocial and psychosexual support both at the family and community levels. However, patient support groups have yet to be established. With this evolution of care into an MDT approach, the trend has been toward delaying reconstructive procedures until the child is of age to participate in a shared decision-making process.

Initial clinical evaluation of patients presenting with DSD is well described (3). While most of the relevant and recommended tests became progressively available within the course of the study period, their high cost made routine use prohibitive. Reports from other resource-limited settings showed that poverty was the main factor affecting long-term outcomes of patients with DSD (20). The majority of our patients rely on NHIF to access healthcare. Despite progressive NHIF expansion to provide more funding for operative procedures and investigative studies, tests considered key for patient workup (Karyotype and Biochemical assays) are yet to be incorporated. In view of this, there was a heavy reliance on diagnostic procedures (genitoscopy/laparoscopy) and histopathologic analysis of gonadal biopsies to aid in diagnosis. Minimally invasive diagnostic and therapeutic procedures have replaced the use of imaging modalities such as ultrasound and MRI, which, in our context, are either unreliable due to user variability or financially prohibitive. A similar pragmatic approach is in practice in other parts of Africa (11). None of our patients was able to undergo a complete diagnostic workup required for a comprehensive diagnosis. Similar challenges have been reported from other centers in the country (21). The gains of this minimalistic approach notwithstanding, it is our assertion that at the very least karyotyping, 17-hydroxyprogesterone (17-OHP) and anti-Müllerian hormone (AMH) testing should be incorporated as mandatory first-line investigations for all patients presenting with atypical genitalia. These would ideally be incorporated into a "DSD diagnostic package" offered by NHIF at a center of excellence.

Conclusion

Management of patients with DSD poses a challenge to healthcare providers across the globe. The gradual evolution of patient management with incorporation of MDTs and progression toward delayed surgery is evident in the current study. However, the unique setting in LMIC presents challenges not typically encountered within high resource settings that may necessitate alteration of standards of practice. There is indeed a need to set up regional centers of excellence, public awareness programs, and healthcare personnel training programs for optimal management of these patients in LMICs.

Conflict of interest

None to disclose

Author contributions

All other authors contributed equally in the conceptualization and writing of the first draft to reviewing and editing the original draft.

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