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Clinical Study

Challenges and Outcomes of 46,XY Disorders of Sex Development: An Analysis of 30 Cases from Senegal

Ndèye Aby Ndoye[1,2], Lissoune Cissé[3], Aloïse Sagna[1,2], Cheikh Diouf[4,5], Ousmane Guèye[1], Faty Balla Lo[3], Fatou Sy[1], Doudou Gueye[1], Pape Alassane Mbaye[1,2], Oumar Ndour[2,6], Gabriel Ngom[1,2]

[1] *Department of Pediatric Surgery, Albert Royer Children's Hospital Dakar, Senegal*
[2] *Cheikh Anta Diop University, Dakar, Senegal*
[3] *Department of Surgery, Pikine National Hospital Dakar, Senegal*
[4] *Assane Seck University, Ziguinchor, Senegal*
[5] *Department of Surgery, Ziguinchor Regional Hospital, Ziguinchor, Senegal*
[6] *Department of Pediatric Surgery, Aristide LeDantec Hospital Dakar, Senegal*

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Posterior hypospadias
Testicular descent

Abbreviations
DHT - Dihydro-testosterone
DSD - Disorders of sex development
HCG - Human Chorionic gonadotropin
PMDS - Persistent Mullerian duct syndrome

Abstract

Introduction: *Optimal management of 46,XY disorders of sex development (DSD) has numerous challenges. The aim of this study was to evaluate the epidemiological, diagnostic, therapeutic and prognostic aspects of 46,XY DSD in Senegal.*

Methods: *A retrospective, descriptive study of patients with 46,XY DSD was done between May 2017 and April 2022. Study parameters included incidence, age at diagnosis, phenotype, etiologies, assigned sex, treatment outcome and morbidity.*

Results: *There were 30 new patients of 46,XY DSD. It represented 28% of all DSD cases, with a hospital frequency of 6 new cases per year. The mean age at diagnosis was 46 months. Female or ambiguous phenotypes were found in 3 cases each. The etiologies were androgen insensitivity (n=5), persistent Mullerian duct syndrome (n=4), gonadal dysgenesis (n=3), male adrenal hyperplasia (n=2), testosterone deficiency (n=2), ovotestis (n=2) and uncertain (n=3). The initially assigned sex was retained in 29 cases (97%). One patient required reassignment to male sex. Psychological support (n=3) and medical treatment (n=4) were needed in a few cases. Gonadal surgery and masculinizing genitoplasty were done in 13 (43%) patients. Post-genitoplasty morbidity was observed in 6 cases (46%).*

Conclusion: *46,XY DSD are rare disorders of diverse etiologies. Proper management with a multidisciplinary team can improve treatment outcomes.*

INTRODUCTION

Disorders of Sex Development (DSD) refer to a group of congenital conditions in which there is a discrepancy between chromosomal, gonadal, and phenotypic sex.[1] These disorders are classified as per the Chicago Consensus into 3 categories based on karyotype: sex chromosome DSD, 46,XY DSD and 46,XX DSD. This study specifically focuses on 46,XY DSD characterized by male chromosomal pattern with atypical male genitalia.

The clinical presentation of 46,XY DSD can vary widely, ranging from severe forms of ambiguous genitalia (e.g. female-like external genitalia with intra-abdominal testes) to more subtle manifestations such as hypospadias. The variable phenotypic expression contributes to the discrepancies in the reported prevalence rate of 46,XY DSD, as its definition vary depending on the inclusion of certain forms, such as hypospadias, in different clinical frameworks.[2]

Scientific research on 46,XY DSD has lead to better understanding of their pathogenesis.[2] Etiologically, 46,XY DSD can result from genetic aberrations affecting the formation of the testes, abnormalities of testosterone secretion, defects in the synthesis of dihydro-testosterone (DHT), or mutations in androgen receptors leading to partial or complete androgen insensitivity.

The management of 46,XY DSD is complex and requires a multidisciplinary approach involving pediatric surgeons, clinical psychologists, endocrinologists, geneticists and community nurses. This 'team-based care' model ensures both the medical and psychosocial needs of the patient are adequately addressed, fostering optimal outcomes. Still, management of these conditions poses numerous challenges, particularly in Africa, where diagnostic delays are common due to financial and sociocultural barriers. This disorder remains an enigma to many medical practitioners that early diagnosis is often severely affected. Consequently, many children may already have been raised as females by the time of first consultation with a specialist. This poses significant challenges in deciding the future sex of rearing. Surgical treatment is often necessary in this context, with anatomical correction being the primary concern of adolescent boys and their parents. Management of DSD remains intricate, relying on the definitive etiological diagnosis, functional capacity of the genital organs, feasibility of surgical reconstruction and the need of long-term hormonal supplements. Additionally, factors such as the age at therapeutic intervention, financial resources and sociocultural environment must be carefully considered. 46,XY DSD also pose a significant psychological burden to the affected children and their families. In our settings, DSD remains a psychosocial emergency.

The aim of this study was to explore the demographic, diagnostic, therapeutic and follow-up aspects of 46,XY DSD in pediatric patients at the Albert Royer Children's Hospital, Senegal.

PATIENTS AND METHODS

We conducted a retrospective descriptive study spanning over five years, from May 2017 to April 2022. Patients aged 0 to 16 years, treated for 46, XY DSD in the Department of Pediatric Surgery at Centre Hospitalier National d'Enfants Albert Royer (CHNEAR) were included in the study. A karyotype was done for all included patients, confirming the diagnosis of 46,XY DSD. The etiologies of DSD were classified using the Chicago Classification. Diagnostic workup of the study group is shown in the table-1. Those who did not have minimum essential assessment and those who did not give consent (n=8) were excluded.

Demographic parameters studied were frequency of diagnostic categories, age at the recognition of anomaly, circumstances of the discovery of abnormality, age at initial consultation, geographical location of patients, and assigned sex. *Diagnostic parameters* covered personal and family medical

histories, signs of physical examination, hormonal profiles, features of abdominopelvic ultrasound, diagnostic findings of surgical explorations, histopathological examinations following biopsies, and identified etiological factors. *Therapeutic parameters* included the delay before surgery and nature of surgical intervention (gonadal surgery, genitoplasty or other surgeries). *Evaluation parameters* focused on the types of complications observed during follow-up.

Table 1. Diagnostic work-up of 46,XY DSD†

- Peripheral blood karyotyping
- Abdomino-pelvic ultrasonography
- Hormonal assays
  - Testosterone
  - Follicle Stimulating Hormone (FSH)
  - Luteinizing Hormone (LH)
  - Anti-Mullerian Hormone (AMH)
  - Cortisol
  - 17-OH progesterone
- HCG Stimulation tests*
- Genitography*
- Diagnostic Laparoscopy ± Gonadal biopsy*
- Genital endoscopy (prior to feminizing genitoplasty)

DSD-Disorders of sex development; HCG-Human Chorionic Gonadotropin.
** Done in selected cases when indicated*
† Ratio of Testosterone to Dihydroxy-testotserone was not done in our center due to financial constraints. Thus, we could have missed some of the 5α-reducatse deficiency disorders

RESULTS

Demographic aspects

Thirty patients with 46,XY DSD were enrolled over a period of five-year period, averaging 6 new cases per year. This represented 28.3% of all DSD cases diagnosed during this period. Genital abnormality was noticed at birth in 26 cases (87%) and at a later age (one each at 5, 7, 8 and 9 years) in 4 cases. The anomaly was identified by parents in 20 cases (67%) and by medical or paramedical staff in 10 (33%). The mean age at first consultation was 46 months (range 3 days - 16 years).

Fourteen patients were from Dakar (the capital city and the location of our hospital), 15 were from other regions of Senegal, and 1 was from another country.

At birth, 23 patients (77%) were assigned with male-sex and 7 (23%) with female-sex. Later, two were reassigned to male-sex by their parents even before medical consultation.

Consanguinity among parents was present in 11 cases (37%), including first-degree consanguinity in 2 (7%), second-degree in 7 patients (23%) and unspecified linkage in 2 (7%).

Table 2. Clinical features at presentation in 46,XY DSD patients

Parameter		**n (%)**
Phenotype	Male	24 (80%)
	Female	3 (10%)
	Ambiguous	3 (10%)
Penile size	Micropenis	20 (67%)
	Well-developed*	10 (33%)
Genital Orifice	Single	27 (90%)
	Two	3 (10%)
Urethral Meatus	Apical	1 (3%)
	Peno-scrotal	21 (70%)
	Perineal	8 (27%)
Cryptorchidism	Unilateral	17 (68%)
	Bilateral	8 (32%)
	Inguinal	12 (48%)
	Intra-abdominal	13 (52%)
Penile Curvature		12 (48%)
Asymmetric Genital Folds		2 (8%)
Scrotal Cleft		19 (63%)
Signs of Puberty		3 (10%)

** Four had penile curvature*

Diagnostic Aspects

Clinical features at presentation and final diagnosis are summarized in Tables 2 and 3 respectively. All the patients underwent abdomino-pelvic ultrasound, which identified Mullerian remnant in 4 (13%). Hormone assay was performed in 16 cases (53%), with elevated plasma levels of testosterone being the most frequently observed abnormality that was present in 6 patients (37%). Diagnostic surgical exploration was done in 13, including seven laparoscopic explorations. (Fig.1) There were 2 cases of ovotestis. (Fig.2)

Table 3. Final diagnosis of 46,XY DSD

Etiology*	**n (%)**
Gonadal Dysgenesis	3 (10%)
Androgen Insensitivity	5 (17%)
Persistence of Mullerian Remnants	4 (16%)
Testosterone Synthesis Disorder	2 (7%)
Ovotestis	2 (7%)
Adrenal Hyperplasia	2 (7%)

** See footnote of Table-1 regarding the diagnosis of 5α-reducatse deficiency disorders.*

Therapeutic Aspects

One patient (3%), who was initially raised as a female, required sex reassignment at one month of age. Initially assigned sex was retained in 29 cases (97%). Psychological support was provided to 3 patients (10%). In 2 cases, parents faced challenges in choosing the sex of rearing.

Four patients (13%) received medical treatment in the form of hormonal supplements that include hydrocortisone plus fludrocortisone in 1, β-HCG in 1, gonadotropin in 1 and testosterone in 1 patient.

Surgical treatment was needed in 26 (87%) cases. The mean time delay of surgical treatment was 18 months (range 3-36 months). Gonadal surgery in the form of orchidopexy and partial gonadectomy were done in 11 and 2 cases respectively. Masculinizing genitoplasty was performed in 13 (43%) patients. Techniques included onlay urethroplasty in 6 patients (46%), Duckett's operation in 1 (8%), Koyanagi's repair in 2 (15%), and two-stage Bracka's operation in 4 (31%). Feminizing genitoplasty and vaginoplasty were performed for the children raised as girls. Endoscopic exploration was used to locate the origin of the uro-genital sinus.

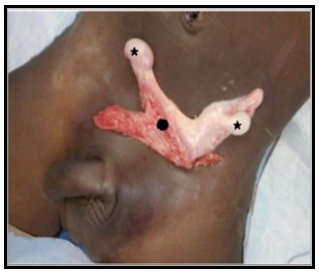

Fig 1. *Crossed testicular ectopia with persistent Mullerian remnant (*Testes; •Mullerian remnant)*

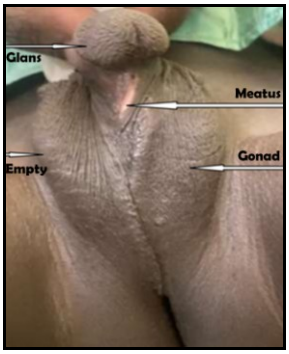

Fig 2. *External genitalia of a 46, XY ovotestis DSD patient showing asymmetric scrotal sac*

Pre-penile scrotum (n=2), penile torsion (n=1) and bifid scrotum (n=4) were also corrected. Hormonal substitution was tailored to the needs of individual patients. Estrogen replacement therapy was started after gonadectomy and testosterone injections are used to support virilization before masculinizing genitoplasty. We do not have access to topical dihydro-testosterone cream in Senegal. Hydrocortisone and fludrocortisone were admini-

stered in 2 boys with congenital adrenal hyperplasia. Human chorionic gonadotropin (HCG) was used to stimulate hormone production in cases of defective testosterone synthesis.

Evaluation Aspects

Postoperative outcomes following masculinizing genitoplasty were favorable in 7 patients. Complications were noted in 6 patients (46%), including fistula in 4, and suture dehiscence in 2. Androgen therapy resulted in an increase of penis size.

DISCUSSION

Demographic Aspects

The frequency of 46,XY DSD varies across studies. In our study, they represented less than a third of all DSD cases. In some published series, a predominance of 46,XY DSD is found to the tune of 53% to 98%.[3,4] These discrepancies may be related to different nosological frameworks. Indeed, anterior hypospadias is not considered a DSD in our center. In our cohort, consistent with several reports, the anomaly was usually discovered at birth.[5,6] But, we noted a delay in consultation that could be explained by delayed referral of patients and socio-cultural factors. In our communities, limited financial resources and the taboo of dis-cussing sex often constrain families from seeking timely medical care.

Diagnostic Aspects

The predominance of male-sex assignment in 46XY, DSD is consistent with the common practice of sex assignment in children with a male phenotype. However, the need of sex reassignment and the challenges associated with it underscore the need for a more early and accurate diagnosis.

Hormonal assay was conducted in 53% of the patients. Plasma testosterone levels were the most common abnormality, present in one third of the patients. Higher percentages are reported in other studies.[4] This discrepancy may be attributed to the fact that our analyses were not necessarily conducted during the mini-puberty period, which is the optimal time for such tests. Delayed diagnosis might have led to hormonal assay being done outside this critical window period, potentially resulting in testosterone levels that are difficult to interpret accurately.

Diagnostic surgical exploration, preferably laparoscopy, is not routinely done in the assessment of 46,XY DSD. However, it is to be done when biopsy of gonads is necessary, especially if ultrasound demonstrates Mullerian remnant.[10,11] Endocrine abnormalities predominate among 46,XY subjects, particularly in those with androgen insensitivity syndrome.[4,6,12,13] Our results are consistent with this observation as there were 5 cases (17%) of androgen insensitivity syndrome. The diagnostic work-up is often suboptimal due to unavailability of surgical facilities and high cost of care. In some cases, the etiology remains unknown due to inadequate workup consequent to the non-availability of genetic and molecular diagnostic tools in our region.

Therapeutic Aspects

In our cohort, only 1 case required reassignment to male sex at 1-month of age. Other pediatric surgeons have reported a reassignment rate of 4 to 12%.[6,14] Psychological support was provided to the parents of 3 patients when they faced the challenges of choosing the sex of rearing. In our communities, however, this concept is often poorly understood or accepted; highlighting the need for healthcare providers to improvise their clinical approach and to collaborate with support groups to provide emotional and social support.[4,15] Lifelong hormonal treatment necessitates meticulous education of patients and their families to ensure treatment compliance.

The mean delay of surgical intervention was often more than a year, which is considered unacceptably long for DSD which has significant psychosocial

impact in our country.[6,15,17] Techniques such as onlay urethroplasty, two-stage Bracka's operation, Koyanagi repair, and Duckett's procedures were used during masculinizing genitoplasties, as per the literature recommendations.[15]

Feminizing genitoplasty was done for the children raised as girls. However, no routine vaginal dilatation was performed at this stage, as they all are young children without a sexual life to maintain the dilations. Vaginal dilatation is planned for the future when it becomes appropriate.

Partial gonadectomy was performed in cases of ovotestis to remove the part of the gonad that did not correspond to the assigned sex. We chose to perform partial gonadectomy rather than total gonadectomy because life-long hormonal treatment is costly and unaffordable for our patients. Although we are aware that partial gonadectomy may be less effective in 46,XY DSD and, that the remaining gonadal tissue may still be at risk of cancer, we opted for partial gonadectomy as an initial approach. We closely monitor them for any complications or malignancy and provide appropriate follow-up care

Evaluation Aspects

In our series, favorable outcome after genitoplasty was noted in more than 50% of cases. However, complications, including suture dehiscence and fistulas, were common and it is consistent with the findings of other studies.[4,18]

MERITS AND DEMERITS

The present study has a few demerits. Firstly, the cohort size is very small. Secondly, we did not estimate the ratio of testosterone to DHT due to non-availability of technology and financial limitations. Thirdly, we do not have long-term follow-up data on sexual function, sperm production, fertility rate and psychological satisfaction with the assigned sex. However, we are intended to follow-up our patients and present the long-term outcome later at an appropriate point of time. Despite these demerits, the present study appears to the first report on 46,XY DSD from Senegal that provides some insight and elementary data necessary for further planning.

Current international standards recommend postponement of the final sex assignment until after puberty when the child can understand and take active part in decision-making. However, in our setting, sex assignment is heavily influenced by socio-cultural factors. Pubertal virilization and the possible need for gender reassignment later were discussed with families on a case-by-case basis, taking into account the available resources. These decisions were always made through multidisciplinary discussions. The goal was to ensure that all stakeholders were fully informed, coordinated and decisions were made consistent and unanimous. This approach is aimed to prioritize the best interests of the child while respecting social, cultural and financial considerations of the family.

CONCLUSION

46,XY DSD is a rare anomaly in Senegal. Its etiological investigations are lengthy and complex. Masculinizing genitoplasty needs a multidisciplinary approach and the therapeutic plan should be tailored to the needs of individual patients. Reconstructive surgery is often necessary, for both functional and psychological reasons. Involvement of commitment health-care professionals as well as patient family is essential for optimal outcome.

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Address for communication: *Dr. Ndèye Aby Ndoye,*
Email: aby_ndoye@yahoo.fr

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