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Original Research Article

Clinical profile of patients with 46 XY disorders of sex development: a single centered experience

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ABSTRACT

Background: XY disorders of sex development are a complex entity that needs medical attention from childhood to adolescence and throughout life. The aim of the study was to analyze retrospectively the medical records of subjects with 46 XY disorders of sex development (DSD) and characterize their clinical profile and management course in a tertiary care centre.
Methods: 32 subjects with 46 XY DSD attending Endocrinology OPD / Gynecology between 2010 to 2020 were enrolled in the study. Data collected includes age at presentation, symptoms, sex of rearing, phenotype, external masculinisation score (EMS), karyotyping, gonadal features like location and histopathology, psychosexual domain and their management and follow up. Statistical Analysis: The mean and standard deviation was calculated for normally distributed data.
Results: The mean (SD) age of all study subjects (n=32) were 15.5 ± 5.32 years. 46 XY DSD included cases of complete gonadal dysgenesis (n=6), mixed gonadal dysgenesis (n=6), complete androgen biosynthetic defects (n=9), partial gonadal dysgenesis (n=2), 5-alpha-reductase type 2 deficiency (n=8) and 17 betahydroxysteroid deficiency (n=1). The most common clinical presentation was for primary amenorrhea followed by genital ambiguity and virilisation in females. Resection of testis at the earliest or a biopsy of the testis if resection is postponed in a female sex assigned 46 XY DSD is favored. Male sex assigned 46 XY DSD needs corrective surgeries and orchidopexy for undescented viable testis with periodic follow up for testicular malignancy.
Conclusions: 46 XY DSD's may shares similarities in their clinical presentation, though age of presentation may be in a wide range. Proper gender assignment, gonadectomy, reconstructive surgeries, hormone replacement and time to time follow up for testicular malignancy in cases where the testes are preserved is the ideal management.

Keywords: Clinical profile, Hormone replacement therapy, Reconstructive surgeries, XY disorders of sex development

INTRODUCTION

46 XY disorder of sex development (DSD) consists of spectrum disorders where males are undervirilised due to defective gonadal development, androgen biosynthesis or its androgen action.[1] At birth, they may present with ambiguous genitals, salt wasting crisis, undescented testis or absent testis. A few cases may remain undetected until they reach puberty. At puberty they present as primary amenorrhea in girls or undervirilisation in boys. Individuals with 46 XY DSD presents to the clinician at different age and the management of DSD is complex and needs a multi-disciplinary approach. In this study, we aim to analyze retrospectively the medical records of subjects with 46 XY DSD and characterize clinical features and study their management issues from a tertiary care center.

METHODS

The study was conducted in the department of Endocrinology in our tertiary care hospital between 2010 to 2020 after receiving approval from the ethics committee of the institute HEC.No.05/18/2020/MCT. All subjects who had been seeking treatment for disorders of sex development were collected from records library. Individuals who had a karyotype 46 XY disorder of sex development (DSD) were enrolled for the study. Our study included 32 subjects with XY DSD. XY DSD included complete gonadal dysgenesis (CDG), partial gonadal dysgenesis (PGD), 45,X/46 XY mosaicism or mixed gonadal dysgenesis (MGD), androgen biosynthetic defects [(5-alpha reductase deficiency and 17 betahydroxysteroid deficiency (17β-HSD3)] and complete androgen insensitivity syndrome (CAIS). Clinical characteristics collected included age at presentation, clinical symptoms, sex of rearing, phenotype, external masculinisation score (EMS), karyotyping, MRI- abdomen and pelvis, hormonal profile, location of gonads and the type of internal ducts based on the laparoscopic or laparotomy findings, histopathology of the gonads, psychosexual domain and the management mode. 46 XY CGD was diagnosed in an individual with female phenotype, complete absence of testicular tissue (streak gonad on histology) with the presence of normal or rudimentary Mullerian structures. 46 XY PGD was diagnosed as dysgenetic testis (on histology) with genital ambiguity with varying degree of wolffian or / and Mullerian ducts. MGD was diagnosed based on genital phenotype, gonadal phenotype and mosaic 45, X/46, XY karyotype. Genital phenotype included from female external genitalia, mild clitoromegaly or ambiguous genitalia. Gonadal phenotype included streak gonads in one side and a dysgenetic testis to normal testis in other side. Androgen biosynthetic defects (ABD) were diagnosed based on genital phenotype, gonadal position and ratio of principle hormone to its precursor. In hCG stimulation test baseline blood samples were collected in fasting for total testosterone. hCG was administered deep intramuscular for three consecutive days in a dose based on the age of the patient (age < 1 year 500 IU per day hCG, age 1-10 years 1000 IU per day and age >10 years 1500 IU per day). Blood samples were collected 24 hours after the third dose of total testosterone (T), dihydrotestosterone (DHT) and androsteinedione (A). Ratios of stimulating hormones T/DHT ratio >20 indicates steroid 5-alpha-reductase type 2 enzyme deficiency, while a T/A ratio <0.8 is suggestive of 17β-HSD3 enzyme deficiency.[2] Androgen receptor mutation analyses were not available in the center to diagnose androgen insensitivity. CAIS was diagnosed based on female phenotype with 46 XY karyotyping with gonads being normal testis on histology and positive androgen insensitivity test (AIT). AIT is done with oral stanozolol (0.2mg/kg/day) and nadir levels of sex hormone binding globulins at day 5 to 8 days from 93-97% indicate CAIS and not an androgen biosynthetic defect.[2] No cases of 46 XY DSD with CAH was available. EMS was devised to see the degree of under virilization among the DSD cases.[3]

Statistical analysis

The mean and standard deviation was calculated for normally distributed data. P value <0.05 was considered significant. Results were analysed with the SPSS software 16.

RESULTS

The mean (SD) age of all study subjects (n=32) was 15.5 ± 5.32 years (range 2- 28 years). There were six cases of CGD, six cases of MGD, nine cases of CAIS, two cases of PGD, eight cases of 5-alpha-reductase type 2 enzyme deficiencies and one case of 17β-HSD3 enzyme deficiency. The most common clinical presentation was primary amenorrhea (n=12, 38%) followed by genital ambiguity (n=9, 28 %), clitoromegaly (n=4, 12, %), primary infertility (n=6, 19%) and gynecomastia (n=1, 3%). 22 children were assigned and raised as female whereas 10 children as males at birth Genital ambiguity was noticed among androgen biosynthetic defects and one case of MGD. Genital ambiguity was in the form of isolated penile hypospadia, bifid scrotum, chordee with hypospadia and perineoscrotal hypospadia with blind vaginal pouch. A child diagnosed as 17β-HSD3 enzyme deficiency presented with gynecomastia at puberty. The mean height (SD) of study subjects was 148 .1 ± 8.2 cm. Among all only one subject with MGD had short stature (height 128 cm, SDS= - 3.24). The mean EMS score (SD) was 3.8 ± 3.3. All patients underwent a psychosexual assessment after diagnosis Table 2. Prior to gonadectomy all subjects underwent counselling to decide on the age preferences. Bilateral gonadectomy was done among CGD, MGD, CAIS and PGD who wished to continue as females. One case of MGD and all cases of ABD wished to continue as males. MGD who wished to continue as male (Number 12) underwent unilateral gonadectomy of intra-abdominal gonad in view of possible streak gonad non-functioning which has a high chance of malignancy and inguinal testis was biopsied and confirmed as testis and later underwent orchidopexy. Descended gonads are considered testis and hence in children with ABD scrotal gonads were considered testis even without histology. MGD male child and ABD children underwent corrective surgeries for hypospadia, correction of chordee and orchidopexy. The child with gynecomastia was started on with tamoxifen and found improvement. The surgical procedure was undertaken after multidisciplinary counselling. Children who completed 12 years among CGD, MGD, PGD and CAIS were started on estrogen therapy followed by cyclical estrogen and progesterone. Testosterone therapy was given to one child with 17 BHSD3 enzyme deficiency (Number 32) and MGD (Number 12). 5-alpha-reductase type 2 enzyme deficiency subjects were only given reconstruction surgeries and all had normal serum testosterone levels.

Table 1: The characteristics of children with 46 XY DSD (n=32).

Age of presentation (years)	Sex assigned	Initial presentation	karyotype	Gonadal Location Right	Gonadal Location Left	EMS	Gonadal Tissue Type Right (histology)	Gonadal Tissue Type Left (histology)	Diagnosis	Surgery done
14	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
14	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
14	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
14	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
16	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
16	Female	Primary Ammenohrrea	46XY	AB	AB	1	Streak	Streak	CGD	Bilateral gonadectomy
4	Female	Clitoromegaly	45X/ 46XY	AB	AB	4	Streak	DT	MGD	Bilateral gonadectomy
8	Female	Clitoromegaly	45X/ 46XY	AB	AB	4	Streak	DT	MGD	Bilateral gonadectomy
10	Female	Clitoromegaly	45X/ 46XY	AB	AB	4	Streak	DT	MGD	Bilateral gonadectomy and clitoral recession
12	Female	Primary Ammenohrrea	45X/ 46XY	AB	AB	4	Streak	DT	MGD	Bilateral gonadectomy
14	Female	Clitoromegaly	45X/ 46XY	AB	AB	1	Streak	DT	MGD	Bilateral gonadectomy
16	Male	Ambigious genitals	45X/ 46XY	AB	ING	6.5	DT	Streak	MGD	Right gonadectomy with left orchidopexy.
18	Female	Primary Ammenohrrea	46XY	AB	ING	1.5	Testis	Testis	CAIS	Bilateral gonadectomy
18	Female	Primary Ammenohrrea	46XY	ING	ING	2	Testis	Testis	CAIS	Bilateral gonadectomy
18	Female	Primary Ammenohrrea	46XY	ING	ING	2	Testis	Testis	CAIS	Bilateral gonadectomy
20	Female	Primary infertility	46XY	ING	ING	2	Testis	Testis	CAIS	Bilateral gonadectomy
20	Female	Primary infertility	46XY	ING	ING	1	Testis	Testis	CAIS	Bilateral gonadectomy
20	Female	Primary infertility	46XY	ING	ING	2	Testis	Testis	CAIS	Bilateral gonadectomy
22	Female	Primary infertility	46XY	AB	AB	1	Testis	Testis	CAIS	Bilateral gonadectomy
24	Female	Primary infertility	46XY	ING	AB	1.5	Streak	Streak	CAIS	Bilateral gonadectomy
28	Female	Primary infertility	46XY	ING	ING	2	Testis	Testis	CAIS	Bilateral gonadectomy
12	Female	Primary	46XY	AB	IN	1.	DT	DT	PGD	Bilateral

Continued.

Age of presentation (years)	Sex assigned	Initial presentation	karyotype	Gonadal Location Right	Gonadal Location Left	EMS	Gonadal Tissue Type Right (histology)	Gonadal Tissue Type Left (histology)	Diagnosis	Surgery done
		Ammenohrrea			G	5				gonadectomy
16	Female	Primary Ammenohrrea	46XY	AB	ING	1.5	DT	DT	PGD	Bilateral gonadectomy
12	Male	Ambigious genitals	46XY	S	S	9	Testis	Testis	5AR	Chordee correction
12	Male	Ambigious genitals	46XY	S	S	9	Testis	Testis	5AR	Hypospadias correction
12	Male	Ambigious genitals	46XY	S	S	10	Testis Primary Ammenoherea	Testis	5AR	Hypospadias and chordee correction
12	Male	Ambigious genitals	46XY	S	S	9	Testis	Testis	5AR	Hypospadias and chordee correction
12	Male	Ambigious genitals	46XY	S	S	9	Testis	Testis	5AR	Chordee correction
12	Male	Ambigious genitals	46XY	S	S	8	Testis	Testis	5AR	Hypospadias and chordee correction
16	Male	Ambigious genitals	46XY	S	S	11	Testis	Testis	5AR	Hypospadias correction
16	Male	Ambigious genitals	46XY	S	S	11	Testis	Testis	5AR	Hypospadias correction
14	Male	Gynecomsatia	46XY	S	S	8	Testis	ING	17BHSD	Hypospadias correction

Table 2: Psychosexual assessment (n=32).

Age of presentation (years)	Sex assigned at birth	Gender identity	Gender role	Sexual orientation
14	Female	Female	Female	Heterosexual
14	Female	Female	Female	Heterosexual
14	Female	Female	Female	Heterosexual
14	Female	Female	Female	Heterosexual
16	Female	Female	Female	Heterosexual
16	Female	Female	Female	Heterosexual
4	Female	Female	Female	Heterosexual
8	Female	Female	Female	Heterosexual
10	Female	Female	Female	Heterosexual
12	Female	Female	Female	Heterosexual
14	Female	Female	Female	Heterosexual
16	Male	Male	Male	Heterosexual
18	Female	Female	Female	Heterosexual
18	Female	Female	Female	Heterosexual
18	Female	Female	Female	Heterosexual
20	Female	Female	Female	Heterosexual
20	Female	Female	Female	Heterosexual
20	Female	Female	Female	Heterosexual
22	Female	Female	Female	Heterosexual
24	Female	Female	Female	Heterosexual

Continued.

Age of presentation (years)	Sex assigned at birth	Gender identity	Gender role	Sexual orientation
28	Female	Female	Female	Heterosexual
12	Female	Female	Female	Heterosexual
16	Female	Female	Female	Heterosexual
12	Male	Male	Male	Heterosexual
12	Male	Male	Male	Heterosexual
12	Male	Male	Male	Heterosexual
12	Male	Male	Male	Heterosexual
12	Male	Male	Male	Heterosexual
12	Male	Male	Male	Heterosexual
16	Male	Male	Male	Heterosexual
16	Male	Male	Male	Heterosexual
14	Male	Male	Male	Heterosexual

DISCUSSION

The development of the male sex is as a result of the interplay between products of SRY genes located on the Y chromosome.[4] Bipotential gonad differentiates into testis followed by development of internal wolffian ducts and external male genitalia. Sertoli cells are the earliest testicular tissue to develop and it secrete anti-Mullerain hormone (AMH) around 6 to 7 weeks of gestation.[5] AMH cause regression of Mullerian ducts. Leydig cells from the fetal testis produce testosterone, which promotes the development and differentiation of the Wolffian ducts like epididymis, seminal vesicle and vas deference.

The external genitals and prostate development occur under the influence of 5- hydrotestosterone (5HT). Any insult at the testicular development, androgen production or its action leads to a broad range of clinical presentation called 46 XY DSD.

46 XY CGD are born with female phenotype. They have normal height to tall stature with no breast, pubic or axillary hair developed.

They usually present at adolescent as primary amenorrhea. They don't virilise at puberty due to the complete absence of testicular function. They have Mullerian structures due to absence of AMH. On the other hand subjects with 45,X/46,XY or MGD and PGD may have a spectrum of genital phenotype. The spectrum of genital phenotype depends on the degree of testicular function. Children with MGD present as ambiguous genitals at birth, a female child virilising before or at puberty, features of turner's stigmata or rarely as primary amenorrhea.[6] The age of presentation may be wide unlike CGD who tend to present during puberty due to amenorrhea. In addition, subjects with MGD may present with Turners stigmata which include growth failure, cardiac and renal anomalies. [7]

Individuals with CGD, MGD and PGD are at high risk to develop gonadal tumors which arise from dysgenetic gonads. The risk of gonadal malignancy is 18 % among MGD, 30 % among CGD and 54% among PGD.[8, 9] This compels the need for early gonadectomy in this group of patients. Gender assignment depends on patient choice and based on the internal and external urogenital anatomy. In our series all cases of CGD, PGD and five cases of MGD were assigned and raised as females and they wished to continue so. All cases of CGD, PGD, CAIS and one five cases of MGD wanted to continue as females and underwent bilateral gonadectomy and feminising hormones were started in who have completed 12 years of age. One case of MGD (number 9) underwent clitoral recession (clitoral size 4 cm) and other cases of MGD with clitoromegaly were monitored, and they had a spontaneous resolution of clitoral size after gonadectomy. One case of MGD (number 12) who was raised as a male and had a preference to female partner underwent unilateral right gonadectomy with left inguinal testis biopsy and orchidopexy. This case had suboptimal levels of total testosterone levels (128 ng/dl) and hence started on testosterone therapy.

All the CAIS subjects presented as the absence of menstruation despite normal developed breast and scanty pubic hair. This presentation has been the classic description. CAIS subjects had testis either located in the abdomen or in inguinal region. After understanding the gender preference subjects with CAIS underwent bilateral gonadectomy.

The timing of gonadectomy is a question yet to be solved. A study by Liu et al has shown the chances of gonadal tumors like gonadoblastoma is as high as 30 % by the age 20 years.[10] On the other hand Cools et al showed that there were no chances of development of testicular tumors or even carcinoma in-situ and the occurrences of pre- germ cell neoplasia in situ (pre-GCIS) lesion was only 14% by 16 years of age.[11,12]

Learning these data from studies on CAIS it would be better to carry out a biopsy of the testis if patients prefer gonadectomy in a later age. Ruling out malignancy by biopsy can help us to defer gonadectomy to later years. One subject presented with gynecomastia (Number 32) and had ambiguous genitals with an EMS of 8. This case was later found to be 17 BHSD deficiencies.

Gynecomastia at puberty is a manifestation of the 17 BHSD deficiency and occurs due to conversion of androstenedione by aromatase in extraglandular tissue.[13] This subject improved with tamoxifen therapy. Also subject with 17 BHSD3 deficiencies (number 32) had lower levels of total testosterone levels were also started on testosterone therapy after complete resolution of gynecomastia.

Lower total testosterone levels are attributed by deficiency of 17 BHSD3 enzyme deficiency which converts A to T. 5alpha reductase 2 enzymes are expressed in prostate and in external genitalia. Its function is the conversion of testosterone to 5 HT. 5HT muscularize external genitals. Its deficiency leads to minor ambiguity of the genitals or hypospadia with or without blind vaginal pouch.

They have normal testis and wolffian ducts. Corrective surgeries for chordee, hypospadia and urethroplasty may be needed depending on the structural defects. We would also like to make a note of the limitation of this retrospective data. The limitation of the study was genetic analysis like androgen receptor mutational analysis and gene mutation for androgen biosynthetic defects were not available. Genetic analysis is essential at times for confirming diagnosis and for genetic counselling.

CONCLUSION

46 XY DSD's may share similarities in their clinical presentation but the age of presentation is wide. The definitive diagnosis needs radiological, laparoscopies and histological evaluation to ascertain the type of internal genital ducts and gonadal type. Management of these patients is multidisciplinary which needs an endocrinologist, gynaecologist, psychologist, pediatrician and clinical genetician. Proper gender assignment, gonadectomy, reconstructive surgeries, hormone replacement and time to time follow up for testicular malignancy in cases where testis are preserved is the ideal management. We may need a long term follow up of these subjects to study the fertility prospects in future.

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