

Gender identity and gender of rearing in 46 XY disorders of sexual development

Arushi Gangaher, Vasundhara Chauhan, Viveka P. Jyotsna, Manju Mehta¹

Departments of Endocrinology and Metabolism and ¹Psychiatry, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Background: Disorders of sexual development (DSD) may pose a challenge to live as a fully-functioning male or female. In this study, we prospectively assessed eleven 46 XY DSD patients who were being treated at our center over the last 8 months for gender dysphoria. **Materials and Methods:** To determine gender dysphoria, age-appropriate gender identity (GI) questionnaires were used. For patients, 12 years and below, parent report GI questionnaire for children was used and for those above 12 years of age, GI/gender dysphoria questionnaire for adolescents and adults was administered. **Results:** Of 11 patients with 46 XY DSD, three were diagnosed with 5 alpha reductase deficiency (5 α RD), two with partial gonadal dysgenesis, three with partial androgen insensitivity syndrome, one each with ovotesticular, complete gonadal dysgenesis, and complete androgen insensitivity. Gender assigned at birth was female in eight and male in three patients. Among the eight reared as female, gender had been reassigned as male in three patients well before the present study was conducted. None of the eleven patients had gender dysphoria at the time of this study. **Conclusion:** Early gender of rearing was seen to be a critical indicator of present GI in our patients except in cases of 5 α RD.

Key words: 46 XY disorders of sexual development, gender dysphoria, gender identity

INTRODUCTION

Disorders of sexual development (DSD) refer to a set of clinical conditions where the chromosomal, gonadal, and anatomical sex is atypical. In 2006, the Lawson Wilkins Paediatric Endocrine Society proposed new a classification of DSD^[1] on the basis of karyotype. DSD in 46 XY is categorised into disorders of gonadal development (gonadal dysgenesis) and disorders of androgen synthesis and action (5 alpha reductase deficiency [5 α RD], androgen insensitivity, 17 β hydroxysteroid dehydrogenase deficiency etc.).

Corresponding Author: Dr. Viveka P. Jyotsna,
Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India.
E-mail: vivekapjyotsna@gmail.com

Sex of rearing can be seen as a promising predictor of gender identity (GI). Sex of rearing can be defined as the phenotypic or gender-specific upbringing by which a child is brought up. It plays a critical role in forming a healthy GI once the child reaches adolescence. For this reason, it is carefully examined in DSD patients.

A healthy GI and the interaction of nature (genetic makeup, physiology, and hormones) and/or nurture (sex of rearing and upbringing) shapes an individual's psychological development. GI represents the core sense of who we are as an individual.^[2] It encompasses the rational and emotive aspects of the core self. Gender role (GR) is an extension of one's GI that encompasses an individual's gender-related attributes, preferences, beliefs, and behaviors that are socio-culturally sanctioned. GR comprises of two gender

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identities that can be chosen typical male or typical female.^[3] Stigma and societal unacceptability may arise if one's GI lies in-between these two points, or if one is dissatisfied with their current GI. Hence, gender can be understood as a broad spectrum concept, rather than as two distinct entities. With regard to gender assignment in such cases, the decision is carefully based upon surgical procedures, hormone replacement options, fertility outcome, and sexual functioning of the patient.^[2,3]

Decisions such as the patient's potential to live in the desired gender, their psychological adjustment postsurgery, quality of life, and psychosocial functioning within their society, and culture is effected by individuals GI. Therefore, this study was planned to assess GI and gender dysphoria in 46 XY DSD patients.

MATERIALS AND METHODS

This is a cross-sectional study. All old and new patients of 46 XY DSD, who were being treated in our outpatient department from April 2015 to November 2015, were recruited, after getting approval from Institute Ethics Committee.

Complete clinical, hormonal and cytogenetic analysis was done for new cases and for old cases; records were checked to establish a diagnosis. Testosterone (T) to dihydrotestosterone (DHT) ratio of >10 was used for the diagnosis of 5 α RD. Diagnosis of 5 α RD was confirmed by the presence of R246Q mutation in one of the three 5 α RD patients who had undergone bilateral gonadectomy in childhood about 18 years back.

Diagnosis of partial gonadal dysgenesis (PGD) was made on the basis of genital ambiguity, low baseline testosterone, poor response to human chorionic gonadotropin (HCG) stimulation, raised serum follicle-stimulating hormone (FSH) levels, size, and echotexture of gonads by radio imaging. The histopathological analysis further confirmed the diagnosis of PGD and also ovotesticular DSD (OT-DSD).

A diagnosis of partial androgen insensitivity (PAIS) was made in patient with ambiguous genitalia, palpable gonads, normal serum testosterone, LH and FSH levels after ruling out other causes of 46 XY DSD by a normal T:DHT ratio and serum testosterone: Androstenedione (T:A) ratio. When reared as female, histological studies postgonadectomy were also used for the confirmation of diagnosis.

Patients being reared as females were diagnosed with complete androgen insensitivity syndrome (CAIS) and complete gonadal dysgenesis (CGD) when they presented

in postpubertal age with unambiguous female genitalia with the presence of bilateral palpable gonads and streak gonads, respectively.

Parents of children who were 12 years and below were administered parent report GI questionnaire for children (PR-GIQ)^[4] to screen their children for gender dysphoria. PR-GIQ is a parent report of assessment of problems in the GI development of children aged 2.5–12 years. It contains 16 questions that cover a range of sex-typical behaviors of each gender. The parent answers each item by rating it on a 5 point scale based on the frequency of occurrence. Lower scores reflect more cross-gendered behavior. A mean score of 2.87 or below for boys and 2.67 or below for girls indicates the presence of gender dysphoria. Specificity rate for this test is 95% for the controls, and sensitivity rate for the probands is 86.8%.

Adolescents above 12 years and adults were screened for gender dysphoria using GI/gender dysphoria questionnaire for adolescents and adults (GIDAA).^[5] GIDAA is a self-administered assessment tool to assess gender dysphoria. Consisting of 27 questions, each item is rated on a 5 point scale. A mean score of 3.00 or below indicates the presence of gender dysphoria for both genders. It displays a strong discriminant validity of 0.97 with 90.4% sensitivity for the GI patients and specificity of 99.7% for the controls.

Male version of these tests was used on patients reared as males and vice versa. Both the questionnaires were translated in Hindi and back translated.

RESULTS

A total of 11 patients were recruited in this study. Age at gender evaluation ranged from 6 to 27 years. Gender assigned at birth was female in eight and male in three. Among eight reared as female, gender had been reassigned as a male in three patients years before the present study was conducted.

None of the eleven patients had gender dysphoria at the time of this study.

On complete evaluation [Table 1] three patients were found to have 5 α RD, two PGD, three PAIS, one each had OT-DSD, CGD, and CAIS.

All three patients with 5 α RD (P.1, P.2, P.3) had ambiguous genitalia since birth. They were assigned female gender at birth. Male gender had been reassigned in these patients at the age of 3, 13, and 17 years, respectively.

Between the two diagnosed with PGD (P.4 and P.5), one had been reared as male and one as female. P.4 being reared as male is on follow-up and is planned for testosterone injections at prepubertal age, as per requirement. P.5, being reared as female, underwent gonadectomy at 3 years of age and is on estrogen replacement therapy for breast development.

Out of three patients diagnosed with PAIS (P.6, P.7 and P.8), one (P.6) was reared as female and two (P.7 and P.8) as males.

Patient P.9 with OT-DSD had gonadectomy done in the past and is on estrogen replacement for the development of secondary sexual characteristics.

Patient P.10 with CGD was reared as female and sought medical attention for primary amenorrhea and no thelarche.

Patient P.11 with CAIS was reared as female and brought to medical attention due to primary amenorrhea and inguinal swelling.

None of the patients, whether raised as males or females or having gender reassignment had gender dysphoria at the time of this study [Table 2].

DISCUSSION

All patients in our study were well-adjusted in their gender assigned at birth, except three with 5 α RD who were reassigned male gender after being reared as females for initial years.

Most patients with 5 α RD are prenatally exposed to normal levels of testosterone, coupled with postnatal virilization; the outcome will most likely result in a male GI during or after adolescence.^[6] Although patient P1 was being raised as a girl, he had been brought for ambiguous genitalia at 3 years of age. Records showed that his psychological evaluation (GI questionnaire for children) done at 3 years revealed male GI. The HCG stimulated testosterone/DHT ratio was found raised. A diagnosis of 5 α RD was made. The parents were informed and with their involvement,

Table 1: Clinical profile of patients

Patient number	Gender*	Primary complaint	Gender reassigned (age in years)	Mullerian structures	Diagnosis
P.1	Female	AG	Male (3)	-	5 α RD
P.2	Female	AG	Male (13)	-	5 α RD
P.3	Female	AG	Male (17)	-	5 α RD
P.4	Male	AG	No	-	PGD
P.5	Female	AG	No	-	PGD
P.6	Female	Primary amenorrhea, hirsutism, no thelarche	No	-	PAIS
P.7	Male	AG	No	-	PAIS
P.8	Male	AG, gynecomastia at puberty	No	-	PAIS
P.9	Female	AG	No	-	OT-DSD
P.10	Female	Primary amenorrhea, no thelarche	No	+	CGD
P.11	Female	Primary amenorrhea and delayed development of secondary sexual characteristics	No	-	CAIS

*Gender: Gender assigned at birth, +: Present, -: Absent, AG: Ambiguous genitalia, 5 α RD: 5 alpha reductase deficiency, PGD: Partial gonadal dysgenesis, PAIS: Partial androgen insensitivity syndrome, OT-DSD: Ovotesticular disorders of sexual development, CGD: Complete gonadal dysgenesis, CAIS: Complete androgen insensitivity syndrome

Table 2: Summary of gender analysis

Patient information	Diagnosis	Age [#] (years)	Gender of rearing	Gender of rearing at time of evaluation	Tests administered	Test findings	PR-GIQ*/GIDAA** scores
P.1	5 α RD	8	Female » male	Male	PR-GIQ	GD (-)	5.00
P.2	5 α RD	17	Female » male	Male	GIDAA	GD (-)	5.00
P.3	5 α RD	20	Female » male	Male	GIDAA	GD (-)	5.00
P.4	PGD	9	Male	Male	PR-GIQ	GD (-)	4.90
P.5	PGD	19	Female	Female	GIDAA	GD (-)	5.00
P.6	PAIS	20	Female	Female	GIDAA	GD (-)	4.77
P.7	PAIS	6	Male	Male	PR-GIQ	GD (-)	4.71
P.8	PAIS	17	Male	Male	GIDAA	GD (-)	4.74
P.9	OT-DSD	18	Female	Female	GIDAA	GD (-)	5.00
P.10	CGD	27	Female	Female	GIDAA	GD (-)	4.90
P.11	CAIS	22	Female	Female	GIDAA	GD (-)	4.70

*Age: At time of psychological evaluation, *Gender reassignment, *A mean score of 3.00 or below indicates the presence of gender dysphoria, **A mean score of 2.87 or below for boys, and 2.67 or below for girls indicates the presence of gender dysphoria; GD (-): No gender dysphoria, GIDAA: Gender dysphoria questionnaire for adolescents and adults, 5 α RD: 5 alpha reductase deficiency, PGD: Partial gonadal dysgenesis, PAIS: Partial androgen insensitivity syndrome, OT-DSD: Ovotesticular disorders of sexual development, CGD: Complete gonadal dysgenesis, CAIS: Complete androgen insensitivity syndrome, PR-GIQ: Parent report gender identity questionnaire

gender was reassigned as male. Thus, before the child started school, the gender was assigned avoiding confusion and making it easier for the patient and family. At the time of this study, the child is 8 years old and has no gender dysphoria as a male. The second patient P2, aged 17 years, was raised as a female for the first 13 years of his life and was brought to our center for ambiguous genitalia. His testosterone/DHT ratio was raised and he had male GI. Gender was reassigned as a male. He is now well-adjusted as a male and showed no gender dysphoria at the time of this study. In a review study of 5 α RD patients reared as females, as high as 63% of the XY patients changed their gender identities from female to male.^[7]

The third patient, P.3, with 5 α RD had undergone bilateral gonadectomy at 2 years of age (reason, not known). He was brought at 17 years of age with gender dysphoria. On gender assessment, he was found to have male GI. Gender reassignment was done and now at 20 years of age, he is well-adjusted as male but is anxious about the absence of facial hair and small phallus. This is in accordance with studies that show that most patients with 5 α RD are prenatally exposed to normal levels of testosterone and this most likely results in a male GI during or after adolescence.^[6] For patient 2 and 3 the main concern was small penile size. DHT cream used as a treatment is not freely available in India.

Our 2 patients of PGD, patient P.4, aged 9, and P.5, aged 19 were reared as male and female respectively and were comfortable with their respective gender identities. In a study,^[8] 11 patients of PGD were asked to evaluate themselves on the experienced degree of masculinity and femininity. Those raised as female reported more femininity and those raised as males reported feeling more masculine. No instance of gender confusion was reported. Hence, assigned sex and psychosocial attributes contribute to the GI of an individual. Though PGD patients have been raised as both males and females,^[9,10] long-term outcome in patients PGD^[11,12] have been recently published and bring forth that male gender assignment is preferred. This could be explained by the prenatal action of testosterone in the brain (which is an important determinant of gender development) and improved surgical reconstructive techniques. Gender should also be guided by GI assessment as a part of the workup.

In the case of PAIS, most infants are assigned male gender at birth. However, if reared as females, genitoplasty, and gonadectomy are advised to avoid virilization.^[13] The timing of gonadectomy and genitoplasty is an area of debate. Our two patients with PAIS, P.4, aged 6, and P.5, aged 17, were both reared as males and had male GI. A review study on PAIS reported that out of 99 individuals with PAIS, only

nine patients had changed their gender.^[14] Initial gender assignment and subsequent gender of rearing were seen to be good predictors of their adult gender identities.^[15]

OT-DSD is a rare condition. Studies show that OT-DSD patients can be reared either as males or females, depending upon socio-cultural influences, external genitalia, and consultation with parents. In a study of seven patients of OT-DSD,^[16] gender assigned by parents was male in five and female in two. In a larger study of 20 patients with OT-DSD,^[17] thirteen were assigned male and seven female gender at birth. Among seven assigned as female, three were later reassigned male gender. Thus male gender assignment was more prevalent. Our patient, P.9 aged 18 years was raised as a female and showed no gender dysphoria at the time of analysis. She had undergone gonadectomy and was on estrogen replacement.

Patients with CGD have unambiguous female genitalia and our patient P.10, aged 27, was no exception. She had been raised as a female and came to medical attention when at puberty she failed to have thelarche and menarche. Baseline FSH was high. For breast development, she was started on estrogen, and when she left it, she started having vaginal bleeding. Ultrasound revealed hypoplastic uterus and doubtful small dysgenetic gonads. She is on estrogen replacement, and no gender dysphoria was found. She has been advised gonadectomy, but due to the stigma attached to the disease, she does not know on what grounds to take leave for gonadectomy.

A recent study assessed 176 individuals with DSD (66 adolescents and 110 adults) on GI. Participants were divided into four subgroups based on their karyotype, absence/presence of androgen effects, and sex of rearing. Results did not indicate an increase in gender dysphoria.^[18]

In studies, examining the psychosocial adjustment of 46 XY DSD patients using adult behavior checklist and WHO-QOL (BREF), it was found that DSD patients scored high on anxiety and depression as compared to the controls.^[19,20] Patient P.2 and P.3 (5 α RD) were anxious about their small phallic length and lack of facial hair. Patient P.4, a case of PGD, has speech and learning problems. P.10 (CAIS) was anxious about her future and stigma associated with her condition. Patient P.6 (CGD), raised as a girl, was anxious about her hirsutism and poor breast development. Her anxiety subsided after gonadectomy and estrogen replacement.

Patient P.10, reared as a girl, diagnosed to be having CGD, is well-educated, employed, and financially independent. She also maintains regular contact with an internet-based DSD support group. However, she expressed concerns

seeking leave for getting gonadectomy done as she did not know on what grounds to take leave as she did not want to reveal her condition in view of the stigma attached to it. She was also worried about her future with regard to sexual relationship and marriage.

Patient P11, a case of CAIS, reared as a girl, who after diagnosis has undergone gonadectomy, is well-adjusted as a female. She is on estrogen replacement for breast development.

Since DSD may limit individuals to live as a complete female or male, in a society that assumes binary gender,^[21,22] XY DSD patients tend to experience anxiety and stress pertaining to their physical characteristics along with a sense of stigma arising from secrecy to hide their condition imposed by families and society. All this can lead to feelings of inadequacy, depression, doubtful self-perception, and identity.^[2]

With respect to gender assignment based on the cause and extent of the defect in 46 XY DSD, there is a lack of uniform guidelines.^[20] Careful follow-up, recording, and documenting of these cases is needed for creating these guidelines. As these patients are rare, collaboration with data collection with follow-up across centers that manage these patients can help to give directions for the future management of these patients. GI scales should be made part of the management of DSD patients decrease mistakes of the sex of rearing, pubertal induction, and genitoplasty that these patients may face.

The psychological assessment of patients with DSD should be viewed as a long-term process rather than a single event.^[23] DSD patients may face social stigma, discrimination, shame, fear, mood disturbances, gender dysphoria, anxiety, and depression. All this can negatively impact their academics, relationships, independence, and future employment opportunities. This can have a debilitating impact on their overall quality of life.

Although, our sample size was small with a spectrum of diagnoses among 46 XY DSD, however, it offers an insight into gender assessment and assignment in 46 XY DSD. Treatment of 46 XY DSD involves gender assignment, information management, communication, the timing of medical interventions, hormonal therapy, and surgery. Medical and psychosocial factors may sometimes result in the desire to change gender later in life.

CONCLUSION

Among these 11 patients with 46 XY DSD, 5 were living as females and 6 as males at the time of this study. GI

was found to be in concordance with the gender in all patients at the time of this study. Gender had previously been reassigned to male in 3 patients who were cases of 5 α RD. No patient whether raised as female, male or having gender reassignment had gender dysphoria at the time of this study.

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Conflicts of interest

There are no conflicts of interest.

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