Long-Term Outcomes in Males with Disorders of Sex Development

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Abbreviations and Acronyms

DSD = disorders of sex development

FSH = follicle-stimulating hormone

GD = gonadal dysgenesis

LH = luteinizing hormone

MSHQ = Male Sexual Health Questionnaire

PAIS = partial androgen insensitivity syndrome

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Study received approval of medical ethics committee at each participating institution.

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Purpose: Indications that the prenatal action of testosterone in the brain is an important determinant of gender development and improved reconstructive techniques have caused a shift in male gender assignments in patients with 46XY disorders of sex development. We report long-term outcome data on psychosexual development and sexual function of these individuals in a cross-sectional study.

Materials and Methods: Physical status of 14 men with a mean age of 25 years with disorders of sex development was assessed by structured interview and physical examination. Psychosexual outcome was evaluated by questionnaires and compared to a control group of 46 healthy, age matched men.

Results: A total of 13 men underwent 1 to 6 (mean 2) genital surgeries. Mean age at first surgery was 2.7 years. Mean penile length was 6.6 cm. All men reported erections and were able to experience orgasms. Ejaculatory dysfunction was reported by 7 men. Mean penile length was 7.9 cm in patients who were able to achieve penetrative intercourse and 4.9 cm in those who were not. Meatus was glanular in 5 patients, coronal in 7 and at the distal shaft in 1. Compared to controls, men with disorders of sex development were less satisfied with the appearance of the penis and scrotum but not with total body image. These patients reported decreased sexual desire and activities.

Conclusions: Outcome in this group of men with disorders of sex development was poor regarding penile length, ejaculation, satisfaction with external genitalia and frequency of sexual activity. Other aspects, such as overall body image and psychosexual functioning, showed no difference from controls.

Key Words: body image; disorders of sex development; follow-up studies; sex reassignment surgery; urologic surgical procedures, male

Disorders of sex development are defined as congenital conditions involving atypical development of chromosomal, gonadal or anatomical sex.[1] The underlying chromosomal constitution of infants with markedly ambiguous genitalia may be 46XY, 46XX or a mosaic pattern. Of patients with disorders of sex development and 46XY hypovirilization syndromes a specific diagnosis can be made in only 20%.[2] Improved reconstructive techniques and observations of gender dysphoria and a wish for a gender role change in patients with 46XY hypovirilization raised as girls resulted in more male sex assignments in the last decades, particularly in patients with

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less severe hypovirilization.[1,3–7] The aim of masculinizing surgery in patients with disorders of sex development is to improve cosmesis and function of the external genitalia, to enable sexual intercourse and to avoid stigmatization. Therefore, it is important to assess the functional and sexual outcomes of these patients. There have been a limited number of outcomes studies in males with disorders of sex development, including those with an undefined 46XY disorder.[5,8–12] However, studies with combined data on urological and in-depth psychological examination in relation to surgical history are scarce. We investigated the long-term physical, functional and psychosexual outcomes in males with disorders of sex development in a cross-sectional study.

METHODS

A total of 37 males older than 14 years with DSD identified at 2 university hospitals between 2007 and 2009 were invited to participate. Of these individuals 14 (37%) participated, including 9 from Erasmus MC Rotterdam and 5 from Radboud University Nijmegen Medical Center. Inclusion was based on diagnosis of DSD and phenotype (ie proximal hypospadias and unilateral/bilateral cryptorchidism). The study was approved by the medical ethics committees of both centers. All participants were informed about the study and signed a written consent form. Participant responses to the Male Sexual Health Questionnaire were compared with those of a control group of 46 male students with a median age of 21.5 years (range 18 to 36) who volunteered to participate in the study.

Data on genital appearance at birth and genital surgeries were retrospectively collected from the medical files. Subsequently participants underwent a urological examination, hormonal analysis and psychological assessment between 2007 and 2009. LH, FSH and serum testosterone levels were determined as described previously.[13]

Surgeries were divided in hypospadias repair and additional procedures. Patients were grouped based on diagnosis. Cases without a molecular diagnosis were classified as undefined 46XY DSD.

Standardized urological examination consisted of visual inspection (general impression, testes, localization and shape of meatus, penile curvature, distortion, penoscrotal transposition) and measurements (testis volume, penile circumference, stretched penile length, self-measured degree of curvature). The examiners had not been involved in the medical care of these patients.

Psychosexual functioning and satisfaction with genital image were assessed by questionnaires and a semistructured interview administered by psychologists not involved in the care of the patients. The MSHQ is a validated, self-administered instrument for assessing problems in the primary domains of erection, ejaculation and sexual satisfaction in men.[14] Aspects of sexual functioning and problems, as well as satisfaction with (surgical) treatment and impact of treatment on psychosexual functioning were addressed in the interview. Satisfaction with body appearance and appearance of the external genitalia was assessed using a 5-point Likert scale.[15]

Comparisons between groups were done using the chi-square test for categorical variables and Student t test for continuous variables. MSHQ scores were compared using a Mann-Whitney U test (not normally distributed). A p value of less than 0.05 was considered significant.

RESULTS

Participants

Of the 38 men invited to participate 14 agreed (response rate 37%). Mean age was 25 years (range 14 to 32). There were no significant differences between participants and nonresponders regarding age ($p = 0.81$), diagnosis ($p = 0.5$) or number of hypospadias repairs ($p = 0.97$).

Characteristics of the participants are presented in the Appendix. Median age at participation was 25 years (range 14 to 38). One patient with 45X/46XY DSD who presented with bilateral cryptorchidism without hypospadias at age 8 months was excluded from the functional and psychosexual analyses. The others had been diagnosed at birth with hypospadias and cryptorchidism. Family history was positive in 3 patients and consanguinity in 2. Based on Dutch reference data for age 21 years, height was below −2 SD in 5 men and borderline (−1.98 SD) in 1.[16]

Of the 6 men with undefined 46XY DSD 1 had a positive family history of proximal hypospadias. This patient was diagnosed with morbid obesity (body mass index 44 kg/m^2), hypergonadotropic hypogonadism and small testes. Semen analysis revealed azoospermia. Medical history consisted of unilateral testicular torsion, utricular cyst and epididymitis. Hormonal analysis, including human chorionic gonadotropin, adrenocorticotropic hormone and gonadotropin-releasing hormone tests, was normal. Genetic analysis of the androgen receptor was negative.

One man with undefined 46XY DSD was suspected of having a 5'-reductase deficiency. Sequencing of the SRD5A2 gene did not demonstrate any abnormalities, but enzyme function was impaired in fibroblasts in vitro. In the remaining 4 patients with undefined 46XY DSD testosterone synthesis disorders were excluded, and sequencing of the androgen receptor gene did not show any abnormalities.

Surgeries and Urological Examinations

A total of 13 men underwent hypospadias correction involving a mean of 2 surgeries (range 1 to 6). Mean age at first surgery was 2.7 years (range 3 months to 6 years). The undefined 46XY DSD group differed from the other diagnostic groups with respect to a larger variation in age at first surgery. No other differences between groups were found. The groups were too small to assign statistical significance. One man with undefined 46XY DSD had undergone 6 surgical procedures for hypospadias repair. One pa-

tient in the mixed GD group did not have hypospadias. Repeat surgery was needed in another patient with mixed GD at age 17. The other surgeries consisted of hypospadias repair in 2 planned sessions.

Additional procedures are listed in table 1. Both patients with PAIS had undergone gynecomastia correction, of whom 1 needed correction of recurrence at 1.5 years. Gonadectomy was performed in 4 patients. In the ovotesticular DSD group all patients had a histologically confirmed ovotestis. One of these patients had undergone gonadectomy on the right and orchiopexy on the left side plus biopsy. In 2 patients a streak gonad was found, both of whom had a mosaic chromosomal constitution. Histological review of the gonadal tissue did not reveal signs of malignancy.

The results of the urological examination are listed in the supplementary table (http://jurology.com/). Mean penile length was 6.6 cm (range 4.2 to 10.5), which was below −2.5 SD. Four men had a curvature of more than 10 to 60 degrees during erection. The meatus was glanular in 5 patients, coronal in 7 and on the distal shaft in 1.

Functional Assessment

All men reported erections and were able to experience an orgasm. Abnormal ejaculation was present in 7 men, of whom 3 were on androgen replacement. Two patients experienced dry ejaculations most of the time and 1 had dry ejaculations half of the time. Two men complained about the small amount of ejaculate (a couple of droplets), and 2 experienced weak ejaculation. The 8 men who reported achieving penetrative intercourse had a mean penile length of 7.9 cm, which was significantly greater than in the 4 not achieving penetrative intercourse (4.9 cm, $p = 0.028$).

Serum LH, FSH and testosterone measurements demonstrated hypergonadotropic hypogonadism in the 3 patients with mixed GD (LH 18.7, 22.3 and 27.3 IU/L, FSH 46.6, 66.0 and 54.4 IU/L and testosterone 7.0, 4.2 and 2.7 nmol/L, respectively). All of these patients were on testosterone replacement therapy (Sustanon® 250 or testosterone undecanoate) after gonadectomy and thus had signs of under treatment. The remaining patient (with ovotesticular DSD) who was on testosterone replacement after gonadectomy had slightly increased FSH values (11.1 IU/L) but normal LH (1.15 IU/L) and testosterone values (19.5 nmol/L). The two patients with PAIS had high levels of LH (19.8 and 12.4 IU/L) and testosterone (63.7 and 28.7 nmol/L). The 6 men with undefined DSD had normal male values (2 patients) or increased FSH values and normal LH and testosterone levels (4). There was no relationship between libido and testosterone values ($p = 0.892$).

Men with sufficient urine volume (greater than 100 cc) during flow measurement (8 patients) showed a mean maximum flow rate of 20.6 ml per second. One patient had a plateau curve and the others had a normal curve.

Men with DSD were significantly less satisfied with the appearance ($p < 0.001$), color ($p < 0.001$), thickness ($p = 0.03$) and size (flaccid $p < 0.001$ and erect $p < 0.001$) of the penis, as well as the scrotum ($p < 0.001$) and size of the testes ($p < 0.001$) compared to the control group. Participants were dissatisfied regarding penile size (small), scrotum (asymmetry) and testes (too small). Satisfaction with the amount or appearance of pubic hair did not differ between participants and controls. There was also no difference in satisfaction with secondary sex characteristics (voice, body hair, facial hair, breasts, hips and Adam's apple, $p = 0.489$) and nonsex characteristic body parts ($p = 0.267$) or total body image between participants and controls ($p = 0.098$). Six of the 10 men who answered the question perceived that their sexual development was negatively influenced by their genital appearance. Only 3 men felt they were sexually hampered, especially regarding penile size.

Psychological Assessment

Detailed psychosexual functioning was assessed in 11 participants. One adolescent (14 years) had no sexual experience, and 1 man (19 years) refused to

Table 1. *Surgical procedures*

	PAIS	Mixed GD	Ovotesticular DSD	Undefined 46XY DSD	All Pts
Mean yrs age at first hypospadias repair (range)	3.3 (1.5–5.0)	3 (2.5–3.5)	3.2 (2.0–5.0)	2.3 (0.3–6)	2.7 (0.3–6.0)
Mean No. hypospadias repairs (range)	1 (1–1)	1.3 (0–2)	2 (1–3)	2.5 (1–6)	1.9 (0–6)
No. additional procedures:					
Inguinal herniorrhaphy	2	1	2	2	7
Orchiopexy	2	1	2	2	7
Penoscrotal transpositioning	2	0	0	0	2
Gynecomastia correction	3	0	0	0	3
Gonadectomy	0	2	2	0	4
Fistula repair	1	0	0	2	3
Utriculus excision	0	0	1	1	2
Totals	10	4	7	7	28

complete the MSHQ. Mean age at first coitus was 18 years (range 15 to 23).

Frequency of sexual activity significantly differed between patients and controls. Of the controls 76% had been involved in sexual activities more than 6 times in the month preceding the study, compared to 18% of the patients ($p < 0.001$, table 2). One man (18 years) never had sex due to the absence of sexual desire and arousal, difficulties with erection and orgasm, and lack of a partner. Another man tried to avoid sex as much as possible but gave no further explanation. These statements suggest that both men might be asexual. Others reported difficulties with erection and orgasm (1 patient), low arousal (1) and having no partner (1).

The distress related to the frequency of sexual activity did not differ significantly between patients and controls. The same held true for the proportion of men involved in a steady relationship and satisfaction with sexual relationship. Ten of 11 men had a heterosexual orientation and 1 had a homosexual orientation. No subject reported gender dysphoria. Men with DSD reported on average more difficulties than men without DSD, although the difference did not reach significance except regarding frequency of desire to have sex and problems with firmness of the erection (table 2).

Table 2. *Male Sexual Health Questionnaire results*

	Controls	Pts with DSD	p Value
Sexual frequency/mo:			
No. 0 (%)	0 (0)	3 (27)	
No. 1–6 (%)	11 (24)	6 (55)	
No. more than 6-almost daily (%)	35 (76)	2 (18)	
Mean ± SD frequency	4.0 ± 1.0	2.6 ± 1.4	0.002*
Mean ± SD distress	1.6 ± 0.9	1.8 ± 1.3	0.900
Partner:			
No. with partner (%)	21 (46)	5 (45)	0.805
Mean ± SD satisfaction†	4.4 ± 1.0	4.4 ± 0.8	0.610
Mean ± SD desire:			
Frequency	3.9 ± 0.6	3.3 ± 0.9	0.016*
Level	3.8 ± 0.7	3.4 ± 0.9	0.121
Distress	2.0 ± 0.8	1.9 ± 1.0	0.534
Mean ± SD erection:			
Frequency	4.7 ± 0.6	4.2 ± 1.2	0.155
Frequency of maintaining erection	4.6 ± 0.6	4.2 ± 1.3	0.465
Firmness of erection	4.7 ± 0.6	3.8 ± 1.2	0.006*
Distress	1.4 ± 1.1	1.3 ± 0.6	0.988
Mean ± SD ejaculation:			
Frequency	4.8 ± 0.5	3.7 ± 1.8	0.052
Frequency dry orgasm	1.2 ± 0.6	1.5 ± 1.2	0.342
Frequency delayed ejaculation	1.5 ± 0.7	1.2 ± 0.9	0.222
Force	4.7 ± 0.6	3.8 ± 2.1	0.395
Vol	4.8 ± 0.5	4.2 ± 2.2	0.583
Pain	1.2 ± 0.5	1.4 ± 1.6	0.394
Distress	1.2 ± 0.6	1.3 ± 0.6	0.786

* $p < 0.05$ (2-tailed Mann-Whitney U test).
† Based on 5 items (overall sexual relationship, quality of sex life, frequency of sexual activity with partner, communication about sex with partner and affection during sex).

DISCUSSION

This study evaluates the long-term outcome in males with DSD. We found that mean penile length of postpubertal patients with DSD was below −2 SD and that penile length is correlated to ability to achieve penetrative intercourse. Moreover, abnormal ejaculations are common. The incidence of male gender assignment is increasing due to the awareness of prenatal testosterone effect on gender development, improved surgical techniques and change in attitude toward tolerance of genital anomalies.[1,5,6,12] Generally males with DSD need extensive genital surgery. The severity of hypospadias is correlated with adult penile length.[17] In our study all but 1 patient had a history of hypospadias repair. The patient without hypospadias repair presented with an undescended testis and slight scrotal asymmetry, which triggered chromosomal analysis that revealed 45X/46XY mosaic DSD.

Mean penile length was below −2.5 SD. Mean adult penile length is 13.3 cm (SD 1.6).[18] Reilly and Woodhouse reported the absence of a relationship between sexual functioning and penile length and the ability of men with a microphallus to achieve satisfactory sexual intercourse.[19] In our study the men who were able to achieve penetrative intercourse had a significantly greater mean penile length than those who were unable to do so. Phalloplasty might be an option for men who fail to achieve penetrative intercourse and are dissatisfied with this. However, there is little experience with the procedure, and long-term results are lacking.[20]

Men with DSD were less satisfied than controls with penile appearance, color, size and girth. This finding is in line with other studies demonstrating that small penile size is a major cause of dissatisfaction.[9,21] Sircili et al found that penile length is not significantly related to satisfaction with surgical results.[11] Patients in our study were significantly more dissatisfied with genital image compared to controls, and those with shorter penile length were the most dissatisfied. Interestingly satisfaction with secondary sex characteristics and more neutral body parts did not differ significantly. This finding suggests that genital image and acceptance need special attention during psychosexual counseling of boys with DSD.

Our study confirms that males with DSD in general experience erections and orgasms. However, half of our study population reported abnormal ejaculation, as described previously.[22,23] Schönbucher et al reported an increased incidence of sexual dysfunction and an overall low sexual quality of life in males with 46XY DSD.[24] In our study equivalent numbers of men with DSD and controls were involved in a steady relationship, and satisfaction with the part-

ner and the sexual relationship did not differ between these groups. Men with DSD tended to be less active sexually and reported more erectile problems. However, no significant differences were found in terms of distress or dissatisfaction. The frequency of desire was significantly decreased in men with DSD but not the intensity. Finally, sexual orientation was heterosexual in all but 1 patient, which is in line with previous studies.[9,24]

Our study has some limitations that need to be addressed. First, the study had a cross-sectional design, and some of the data were retrospectively retrieved from medical files. In addition, 61% of the men with DSD declined participation for unknown reasons. Therefore, our data might not be representative of the total group. Furthermore, sexual functioning was measured with the MSHQ, which inquires about sexual problems in the prior 4 weeks only and was designed to assess sexual problems in males. Regrettably there are no validated questionnaires focusing on sexual impairment due to DSD. Lastly the power of statistical analysis was limited due to the small sample size and, therefore, associations might not reach significant difference.

In conclusion, the outcome in this group of men with DSD was poor regarding penile length, ejaculation, satisfaction with external genitalia and frequency of sexual activity. Other aspects such as overall body image and psychosexual functioning showed no difference from controls.

APPENDIX

Patient Characteristics

Pt No.	Karyotype	Diagnosis	Mutation Found	Family History
1	46 XY	PAIS	AR +	Positive
2	46 XY	PAIS	AR +	Positive
3	45X/46XY	mixed GD (streak)	no	Negative
4	45X/46XY	mixed GD (streak)	no	Negative
5	45X/46XY	mixed GD (streak)	no	Negative
6	46 XX	ovotesticular DSD	SRY sequences	Negative
7	46 XX	ovotesticular DSD	no	Negative
8	46 XX/46 XY	ovotesticular DSD	no	Negative
9	46 XY	Undefined 46 XY DSD	no	Negative
10	46 XY	Undefined 46 XY DSD	no	Positive
11	46 XY	Undefined 46 XY DSD	no	Negative
12	46 XY	Undefined 46 XY DSD	no	Negative
13	46 XY	Undefined 46 XY DSD	no	Negative
14	46 XY	Undefined 46 XY DSD	no	Negative

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