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-