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Discordant Sexual Identity in Some Genetic Males with Cloacal Exstrophy Assigned to Female Sex at Birth

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ABSTRACT

BACKGROUND

Cloacal exstrophy is a rare, complex defect of the entire pelvis and its contents that occurs during embryogenesis and is associated with severe phallic inadequacy or phallic absence in genetic males. For about 25 years, neonatal assignment to female sex has been advocated for affected males to overcome the issue of phallic inadequacy, but data on outcome remain sparse.

METHODS

We assessed all 16 genetic males in our cloacal-exstrophy clinic at the ages of 5 to 16 years. Fourteen underwent neonatal assignment to female sex socially, legally, and surgically; the parents of the remaining two refused to do so. Detailed questionnaires extensively evaluated the development of sexual role and identity, as defined by the subjects' persistent declarations of their sex.

RESULTS

Eight of the 14 subjects assigned to female sex declared themselves male during the course of this study, whereas the 2 raised as males remained male. Subjects could be grouped according to their stated sexual identity. Five subjects were living as females; three were living with unclear sexual identity, although two of the three had declared themselves male; and eight were living as males, six of whom had reassigned themselves to male sex. All 16 subjects had moderate-to-marked interests and attitudes that were considered typical of males. Follow-up ranged from 34 to 98 months.

CONCLUSIONS

Routine neonatal assignment of genetic males to female sex because of severe phallic inadequacy can result in unpredictable sexual identification. Clinical interventions in such children should be reexamined in the light of these findings.

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THE CONCEPT OF SEXUAL IDENTITY IN persons with genital malformations has intrigued the medical world since Money and colleagues' pioneering studies of intersex in the 1950s.^{1,2} They later reasoned that an infant's sex could be assigned if corresponding genitalia were constructed during infancy and the child's upbringing corresponded to that sex.³ This concept of sex assignment was especially important for clinicians who were caring for aphallic genetic males, in whom the construction of a functional penis was not feasible.^{1,4-10}

Androgens have long been thought to influence prenatal brain development as well as postpubertal activity, interests, and libido.^{1,10-13} The ability of androgen to act on target tissues in utero could affect subsequent sexual identity. For example, genetic males with androgen resistance, who cannot respond to androgens, identify themselves as female after puberty, whereas genetic males with 5 α -reductase deficiency often see themselves as male, irrespective of whether they were raised as males or females.^{10,14} Genetic females exposed to prenatal androgen are reported to have variable sexual-role behaviors yet rarely develop a male identity.^{12,15} However, follow-up data on sexual identity in children with surgically reassigned sex have been sparse.

Studies of genetic males with cloacal exstrophy may provide insight into the influence of androgen on sex. A devastating developmental defect in pelvic embryogenesis, with an incidence of 1 per 400,000 live births, cloacal exstrophy includes an omphalocele with short-gut syndrome; exstrophy of the bladder, in which a hindgut segment is interspersed with two bladder segments (the "cloaca"); a diminutive hindgut; intussuscepted ileum; wide pubic-symphyseal diastasis; and severe genital inadequacy or atresia. Treatment is medically and surgically demanding, and substantial improvements in critical care and surgery over the past four decades have led to the survival of children with cloacal exstrophy.^{7,16} Neonatal surgical procedures have included separation of the hindgut from bladder components, reconstruction of the bladder, ileostomy, closure of abdominopelvic defects, and in genetic males, female-sex assignment socially, legally, and surgically, including orchiectomy and construction of vulvae. However, the testes are histologically normal,¹⁷ and the phallic atresia occurs despite the presence of normal prenatal androgen levels. Neonatal orchiectomy induces a hypogonadal endo-

crine disorder that precludes postnatal and pubertal androgen surges. The manner in which children with cloacal exstrophy have been treated provides unique opportunities to assess prenatal androgen influences on sexual development in genetic males with female-sex assignment and feminized genitalia in a uniform population of patients.

METHODS

The families of all 16 genetic males in our cloacal-exstrophy clinic who were 5 to 16 years old between 1993 and 2000 agreed to participate. The age range was selected on the basis of the study methods used. Parents provided written informed consent, and subjects provided informed assent. The institutional review board at Johns Hopkins Hospital approved the protocol. Participants were informed that the study assessed psychosocial development in children with the epispadias-exstrophy complex. No subjects were given information about their clinical histories. The study was conducted from June 1, 1993, to August 3, 2001.

Parents had been educated in accordance with the concept that prevention of severe psychosexual dysfunction required reassignment of their genetic male infant to female sex in the neonatal period.^{4,7,8} Fourteen subjects were assigned to female sex at birth: legally, socially, and surgically by means of orchiectomy and construction of vulvae by 2 weeks of age in 13 subjects and by 12 weeks of age in 1 subject. The testes were histologically normal in all 14 when examined after orchiectomy. Parents were instructed to avoid revealing information on their child's sex to anyone at any time, especially to the subject, and were instructed that disclosure of such information might harm the subject's psychosexual development. Two subjects were reared male because the parents refused to have them reassigned to female sex. Table 1 details associated anomalies and the current medical status of all 16 subjects. Follow-up from the time of the initial assessment in the study ranged from 34 to 98 months.

The assessment included six detailed questionnaires that evaluated the subjects' psychosexual development and sexual identity retrospectively and currently. The actual questions overlapped extensively among the questionnaires and assessed multiple topics concerning sexual role, such as the subjects' interest in toys, dolls, clothing, and infants; interest and time spent playing games and participating in various activities; athleticism; aggressive

behaviors; career interests; sexual interests; sex of friends; and whether and to what degree the parents focused on expected behaviors for a daughter.

Questionnaires completed independently by the parents included Bates' Child Behavior and Attitude Questionnaire and the Child Game Participation Questionnaire, each with masculinity and femininity subscores, validated according to the method of Meyer-Bahlburg et al.¹⁸⁻²¹ Two questionnaires administered to the parents were semi-structured and probing in style and included the Gender-Role Assessment Schedule (parent version), validated according to the methods of Meyer-Bahlburg et al. and Lish et al.,²²⁻²⁴ and a psychosexual-history questionnaire written by the first author, which was not validated but which provided further clarification of the parents' and subjects' responses to the study instruments. Questionnaires administered to

subjects included Grellert's structured Childhood Play Activities Questionnaire²²⁻²⁵ and the psychosexual-history questionnaire. The Gender-Role Assessment Schedule and the psychosexual history evaluated, in addition to sexual role, the subjects' sexual preference and stated sexual identity. Questionnaires included from 69 to 90 questions, largely according to the details a given questionnaire assessed. The marked overlap among the questionnaires plus the psychosexual history provided some internal validity for the assessment. Questions have shown good differentiation between male and female responses.²²⁻²⁴

Initial assessment interviews took place over a period of one or two days, lasting about six hours for subjects and four hours for parents. Follow-up clinical information obtained at least yearly through telephone, e-mail, or personal interviews with par-

Table 1. Medical and Surgical Data on the 16 Subjects.

Subject No.	Age at Assessment yr	Associated Medical Problems	Age at Surgery for Incontinence yr	Other Types of or Reasons for Major Surgeries
1	11	Left tibia-fibula agenesis with resulting prosthesis	5	Stoma revision, nephrolithotomy
2	10	—	11	Ureteral stenosis
3	12	Meningocele, scoliosis	6	Ureteral stenosis, scoliosis
4	11	Meningocele, scoliosis	9	Stoma revision, scoliosis
5	6	Meningocele, leg braces	9	Colostomy revision
6	10	Meningocele, leg braces	11	Scoliosis and clubfoot repair
7	9	Meningocele	11	Two for scoliosis Three for tethered cord
8	11	Meningocele	10	—
9	12	Meningocele, leg braces	—*	—
10	7	Bilateral tibia-fibula agenesis with resulting prostheses	5	Revision ileostomy, excision of vagina
11	7	—	6†	
12	5	Meningocele, mild gait disturbance	5	Heel-cord lengthening
13	7	Meningocele, bilateral tibia-fibula agenesis with resulting prostheses	7	Tethered cord, pelvic osteotomy, vesicolithotomy
14	12	Scoliosis	12	Scoliosis, mastectomies
15	16	—	16	—
16	5	Meningocele	6	—

* The subject did not undergo surgery.

† The subject required two operations.

ents focused on the subjects' sexual identity and preference; children were generally not present when the follow-up telephone calls occurred. Although the follow-up questions were not systematic, in that the number and order of the questions varied considerably among subjects and between follow-up interviews, all included some form of the following questions: "How is your child's health?" "Do you think she or he is happy about being a girl or boy?" "Has she or he mentioned gender preference spontaneously?" "Has she or he stated she or he will grow up as a man or a woman?"

RESULTS

Sexual identity varied among the subjects assigned to female sex. Five persistently declared unwavering female identity. One other subject refused to discuss sexual identity with anyone. Eight declared unwavering male identity: four of these subjects declared male identity spontaneously, at the ages

of 7, 9, 9, and 12 years, although the parents of two persistently rejected these declarations. Four others declared male identity after their parents revealed to them that their birth status was male, at ages 5, 7, 7, and 18 years. Two subjects were reared male and identified themselves as male. Table 2 shows neonatal sexual assignment, sex at initial assessment, and present sex. All subjects were in medically stable condition, although they had had various health problems. All attended regular schools.

Assessments revealed moderate-to-marked male-typical behaviors in all 16 subjects. Table 3 gives examples of the questions in the questionnaires as well as the responses provided by the subjects or their parents. Scores for individual subjects ranged from 1, the most typical female response, to 5, the most typical male response. Only one subject stated that she had never wished to be a boy, and only one subject — who later adopted a male identity — stated a very strong interest in marriage, with interest in marriage being more typical of fe-

Table 2. Sexual Identity of the 16 Subjects.

Subject No.	Age at Initial Assessment <i>yr</i>	Sex Assigned at Birth	Sex at Initial Assessment	Sex at Last Follow-up	Age at Last Follow-up <i>yr</i>	Duration of Follow-up <i>mo</i>
1	11	F	F	F	19	98
2	10	F	F	F	17	86
3	12	F	F	F	17	64
4	11	F	F	F	16	64
5	6	F	F	F	9	38
6	10	F	F	Would not discuss	14	38
7*†	9	F	Declared M	Unclear	16	84
8*†	9	F	Declared M	Unclear	14	59
9*	12	F	M	M	21	98
10*	7	F	F	M	11	38
11	7	F	F	M	10	39
12	5	F	F	M	8	36
13	7	F	F	M	10	35
14	12	F	F	M	20	98
15	16	M	M	M	19	34
16	5	M	M	M	12	83

* The subject spontaneously declared male sexual identity.

† The subject's parents rejected his declaration of male sex.

male responses in childhood.^{23,24} All 16 subjects denied ever having had fantasies about weddings. At the initial assessment, the parents of only four subjects assigned to female sex reported that their child had never stated a wish to be a boy.

The parents of each of the five subjects who were living as females felt that the child in each case was happy being a girl, and occasionally commented about growing up to be a woman. The parents of each of the eight subjects living as male — including the two raised as male — felt that their

child was happy living as a boy. The parents of the six subjects who had transitioned to male sex after having been assigned to female sex at birth stated that each child had been much happier since the transition. All eight subjects living as male occasionally mentioned growing up to be a man. The parents of the three children with unclear sexual identity were uncertain about how their children felt about growing up in either sex, although Subject 8, who was living as a female, had occasionally mentioned growing up to be a man. Only the parents of the

Table 3. Examples of Questions and Responses at Initial Assessment.*

Subject No.	Age yr	Subjects' Responses					Parents' Responses		
		Toy Choice	Rough and Tumble Play	Interest in Marriage	Sex of Friends	Wishes to Be a Boy	3 Favorite Activities, 5–8 Yr	3 Favorite Activities, 5–8 Yr	Played with Dolls
1	11	5	4	5	2	1	Reading, wrestling, music	Fishing, swimming, bob-sledding	4
2	10	4	5	2	4	4	Baseball, swimming, bowling	Swimming, tennis, fishing	5
3	12	4	3	2	2	2	Climbing trees, football, watching movies	Baseball, soccer, skating	4
4	11	4	2	3	3	2	Tennis, reading, playacting	Tennis, swimming, fishing	5
5	6	5	5	4	4	3	Basketball, swimming, bowling	Basketball, baseball, art	5
6	10	5	4	4	3	2	Jumping rope, running races†	Basketball, climbing trees, skating	5
7	9	5	4	4	4	5	Baseball, running races†	Baseball	5
8	11	4	2	3	4	4	Karate, baseball, ice hockey	Hunting, baseball, ice hockey	4
9	12	5	5	5	5	5	Hunting, baseball, football	Baseball, football, basketball	5
10	7	5	5	2	5	5	Baseball, running races, all sports	Football, basketball, baseball	4
11	7	4	5	4	5	4	Soccer, baseball	Soccer, golf, baseball	3
12	5	5	4	5	5	5	Baseball, football, computer games	Baseball, basketball, football	5
13	7	4	5	1	3	5	Basketball, Frisbee, swimming	Climbing trees, cops and robbers, cowboys and Indians	4
14	12	2	3	3	4	5	Camping, hiking	Swimming, softball, football	5
15	16‡	5	5	4	5	—	Ice hockey, soccer, roller hockey	Ice hockey, roller hockey	5
16	5‡	5	5	5	5	—	Soccer, running races†	Soccer	5

* Responses could range from 1 to 5, with 1 being a typical female response and 5 a typical male response.

† This subject was wheelchair-bound.

‡ This subject was raised as a male.

subjects who were living as males stated that their child mentioned sexual preference spontaneously.

The parents of all 14 subjects assigned to female sex stated that they had reared their child as a female. Twelve of these subjects have sisters: parents described equivalent child-rearing approaches and attitudes toward the subjects and their sisters. However, parents described a moderate-to-pronounced unfolding of male-typical behaviors and attitudes over time in these subjects — but not in their sisters. Parents reported that the subjects typically resisted attempts to encourage play with female-typical toys or with female playmates or to behave as parents thought typical girls might behave. These 14 subjects expressed difficulties fitting in with girls. All but one played primarily or exclusively with male-typical toys. Only one played with dolls; the others did so almost never or never. Only one ever played house. Each of the three exceptions represents a different subject. Parents noted substantial difficulty attempting to dress the subjects — but not their sisters — in clearly feminine attire after about four years of age.

Thus, subjects sorted themselves into three groups: those living as females, those living with unclear sexual identity, and those living as males. Subjects 1 through 5, who were living as females, were 9 to 19 years old at the end of follow-up (Table 1). All used unambiguously female names and female restrooms consistently. None had knowledge of her birth status. Four had been taking estrogen for two to six years, although their parents were unclear whether the hormone had any behavioral effects. None had dated. None discussed sexual activity or sexual attractions (whereas three adolescent genetic females with cloacal exstrophy did). Parents noted in follow-up interviews that these subjects were generally content. However, the parents did not want these children to participate in follow-up interviews and answered all follow-up questions themselves.

Three subjects (Subjects 6, 7, and 8) had apparently unclear sexual identity. Identifying herself as a female at the initial assessment at the age of 10 years, Subject 6 subsequently angrily refused to discuss her sexual identity with anyone after learning, at the age of 12, that her birth status was male. After 2½ years of suggestions from her physician, she recently began taking estrogen but continues to refuse to discuss sex. Subjects 7 and 8 have persistently and spontaneously declared their sexual identity as males since the age of nine years, before

the initial assessment. They live as females because their parents have rejected their declarations. Both stated during the initial assessment that they wanted a penis. Both take exogenous estrogen and are intermittently compliant with treatment, and both state that they would prefer to receive testosterone. Both identified themselves as male and used male restrooms when they were away from their families and school.

Eight subjects (Subjects 9 through 16) (Table 1) were living as males. All eight used unambiguous male names and male restrooms consistently. Two were reared as male from birth. The six subjects assigned to female sex as infants who subsequently reassigned themselves to male sex legally changed their birth certificates and school registration to male. Subjects 9 and 10 spontaneously declared themselves male without knowledge of their birth status, at the ages of 12 and 7 years, respectively. Subjects 11, 12, 13, and 14 assumed a male identity after their parents informed them of their birth status, at ages 5, 7, 7, and 18 years, respectively. All eight living as males discussed sexual interests and activity; the four adolescents stated that they were attracted to girls. The three adolescents initially assigned to female sex take testosterone and are compliant with treatment. Because of a severely dysfunctional family, Subject 9 received no testosterone until he was incarcerated in a maximum-security prison for armed robbery at the age of 17 years, yet he dated and was sexually active with girls from the age of 15 years. Two of the three subjects over 17 years of age date girls. All eight subjects desire to undergo surgical construction of a penis.

All subjects living as female expressed difficulty fitting in with female peers (genetic females with cloacal exstrophy did not), although those converting to male sex reported few subsequent social problems with females. All 16 subjects described few difficulties fitting in with males.

DISCUSSION

Cloacal exstrophy is not an intersex condition: aphallia and phallic inadequacy are structural anomalies.^{6-9,16} In 1975, Money reported successful reassignment to female sex of a male toddler who suffered traumatic penile loss.²⁶ The concept of neonatal sexual neutrality subsequently developed, emphasizing postnatal, nonhormonal influences.^{4,5,7,8,15,26} Partly on the basis of this concept, the clinical paradigm of sex assignment in neonates

was fully established by the end of the 1970s, including assignment to female sex of genetic males with severe phallic inadequacy. Yet Imperato-McGinley et al.¹⁴ and Bin-Abbas et al.²⁷ presented case series that appeared to refute this paradigm in children with other diagnoses. In addition, in 1997 Diamond and Sigmundson reported that Money's subject had reassigned himself to male sex after years of marked personal and family conflict.²⁸ The results of other case studies have been contradictory.^{14,27,29-31} Information about the sexual preferences of genetic males with cloacal exstrophy who were assigned to female sex as neonates is sparse. Schober et al. reported their clinical impression that their 14 female-assigned subjects with cloacal exstrophy "all have a feminine typical core [but] masculine childhood role behavior."³² The data of Schober et al. are limited, the ages of their subjects are expressed only as "too young" to be used to determine sexual interests or orientation, and the methods they used are not provided.

In our subjects with cloacal exstrophy, the finding of histologically normal testes at orchiectomy in the neonatal period would imply that the brain developed within a male-typical prenatal hormonal milieu.¹⁷ The neuronal properties associated with Y-chromosome-specific transcription factors SRY and ZFY should be typical for such genetic males as well.^{33,34} However, because of sex-reassignment surgery, postnatal androgen surges could not occur in 13 subjects, occurred for only the first three months of life in Subject 14, and should have been normal only in the 2 subjects raised as males with their gonads in place. Only the two raised as males with gonads in place should have normal pubertal androgen surges. Subjects 1 through 14 were raised as females socially and legally, with surgically feminized external genitalia. The ultimate sexual identity of the 14 subjects assigned to female sex in the neonatal period was unpredictable. The sexual behavior and attitudes of all 16 subjects appeared to reflect strong male-typical characteristics, irrespective of whether they were raised as males or females. Five subjects assigned to female sex at birth maintain this identity and appeared generally content. The sexual identity of the one subject who has angrily refused all discussions on this topic since being told of her male status at birth is concerning. Eight subjects assigned to female sex in infancy declared themselves male, four spontaneously and four others after learning that they were born male. None have veered from these declarations. Thus,

some subjects appear to be able to recognize their male sexual identity regardless of environmental mediators to the contrary—a point that recalls the study by Imperato-McGinley et al. of 18 males with 5 α -reductase deficiency who were raised female but, typical of the syndrome, virilized at puberty, with 17 of the 18 subsequently transitioning to male identity.¹⁴

The divergent sexual outcomes of our subjects highlight issues of clinical concern. First, how might subjects who remained female react if they discover their birth status in the future? Can such information be kept secret? Second, subjects who are living as males or transitioning to male sex appear to be more likely to discuss their sexuality. Third, because nearly all genetic males and females with cloacal exstrophy have normal gonads but require genital construction, castration of males requires lifelong administration of exogenous hormones coupled with the loss of potential fertility. Fourth, the absence or presence of genitalia had no discernible influence on the sex of our subjects. Fifth, probably all males with cloacal exstrophy will need (and want) complete penile construction to function sexually with their chosen partner; such need as well as such function—incomplete as it must be for male orgasm—currently has uncertain implications for psychosexual development during adolescence and adulthood. Finally, no genetic females in our cloacal-exstrophy clinic have demonstrated atypical sexual behavior or sexual confusion.

Several other issues are important in interpreting our data. Medical interventions for cloacal exstrophy vary, are usually complex, and sometimes occurred at subjects' local hospitals rather than at Johns Hopkins. Follow-up interviews were not systematic in that, except for the four questions listed in the Methods section, the content and order of the questions varied among the subjects and between follow-up sessions. Although genetic females with cloacal exstrophy were observed clinically, none were included in the study. Spontaneous sex reassignment in children is very rare, however. Finally, the assessment of phenotypic sex itself may have altered parenting: at various times after the initial study assessment, the parents of four subjects assigned to female sex revealed the subjects' birth status to the subjects, contrary to clinic teaching.

Parental attitude toward child rearing based on sex assignment and parental effectiveness are imponderable variables. Thus, conclusive and retrospective determination of factors that were specific

to individual parents is not possible. Parents provided assurances that they raised their genetic males as girls as well as possible, given behavior that was often seen as being more typical of boys. That 12 subjects had genetically female sisters who did not have atypical sexual behaviors offers some evidence that parents did use female sex-of-rearing practices. The scope of the subject matter and topics addressed by the questionnaires, the consistency of parents' and subjects' responses over a period of years, and longitudinal persistence of the subjects' declarations of their sexual identity suggest the reliability of outcome data.

Prenatal androgens appear to be a major biological factor in the development of male sexual identity in the absence of postnatal or pubertal androgen surges, but we cannot assert that they are the only factor. The specific actions of androgen on the developing brain as well as the specific mechanisms

of the development of male sex itself remain largely unknown, and the epigenetic processes as well as socially mediated influences remain indeterminate.^{5,10,15} The implications of our findings for intersex conditions require further investigation. However, our findings suggest that children who are born genetically and hormonally male may identify themselves as males despite being raised as females and undergoing feminizing genitoplasty at birth. Reassignment of genetic males to female sex because of phallic inadequacy may complicate already complex neonatal conditions. Clinical interventions for such neonates should be reconsidered in the light of these findings.

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