46,XY Intersex Individuals: Phenotypic and Etiologic Classification, Knowledge of Condition, and Satisfaction With Knowledge in Adulthood

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ABSTRACT. *Objectives.* **The objective of this study was to identify and study adults who have a 46,XY karyotype and presented as infants or children with variable degrees of undermasculinization of their genitalia (female genitalia, ambiguous genitalia, or micropenis). Participants' knowledge of their condition, satisfaction with their knowledge, and desire for additional education about their intersex condition were assessed.**

Methods. **Participants were classified according to the cause underlying their intersex condition based on review of medical and surgical records. Knowledge of medical condition, satisfaction with that knowledge, and desire for additional education were assessed with a written questionnaire and a semistructured interview.**

Results. **Patients were ineligible for recruitment because of death (9%), because of developmental delay (12%), or because they were not located (27%). Among the 96 eligible patients, 78% participated. Approximately half of the men (53%) and women (54%) exhibited a good understanding of their history. Fewer women who have a 46,XY chromosome complement and were born with female genitalia were informed about their intersex condition (36% with complete androgen insensitivity syndrome) than were women who were born with masculinized genitalia such as micropenis (80%) or ambiguous genitalia (72%). More women (66%) than men (38%) were satisfied with their knowledge of their medical and surgical history.**

Conclusions. **Almost half of the patients, reared male or female, were neither well informed about their medical and surgical history nor satisfied with their knowledge.** *Pediatrics* **2002;110(3). URL: http://www.pediatrics.org/cgi/content/full/110/3/e32;** ***intersex, hermaphrodite, gender, androgen insensitivity, gonadal dysgenesis, micropenis, patient satisfaction, patient knowledge.***

ABBREVIATIONS. CAIS, complete androgen insensitivity syndrome; CGD, complete gonadal dysgenesis; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AR, androgen receptor; PAIS, partial androgen insensitivity syndrome; 17β-HSD-3, 17β-hydroxysteroid dehydrogenase-3; PGD, partial gonadal dysgenesis; MIS, müllerian inhibiting substance.

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In the mid-1940s, Lawson Wilkins established the world's first pediatric endocrine clinic at the Harriet Lane Home of the Johns Hopkins Hospital, and he has thus been considered the founder of pediatric endocrinology. Wilkins's interest in the study of sex differentiation,[1] coupled with those of his surgical[2,3] and psychological[4,5] colleagues, established Johns Hopkins as a referral center for intersex patients.

Statements from patient activist groups (www.isna.org) and research studies[6] have suggested that adults who are affected by syndromes of abnormal sex differentiation are often poorly informed about their medical and surgical histories by their physicians and parents. Furthermore, some of these individuals express dissatisfaction with how little they understand about their medical condition.

The goals of the present investigation were to identify and study adults who have a 46,XY karyotype and presented to the Johns Hopkins Pediatric Endocrine Clinic as infants or children with variable degrees of undermasculinization of their genitalia. On the basis of the appearance of their external genitalia at birth, patients were classified into 3 groups: 1) external genitalia with a normal female appearance, 2) micropenis without hypospadias, or 3) ambiguous genitalia with perineoscrotal hypospadias. Verification of diagnosis was performed for patients whose condition had previously been diagnosed, and an attempt was made to identify the cause underlying abnormal sex differentiation for patients for whom no diagnosis had previously been established (Table 1). Current gender at the time of study participation was assessed with a written questionnaire. In addition, patients' knowledge of their condition, satisfaction with their level of knowledge, and their desire for additional services from our clinic were assessed. The study of this group of patients is of particular importance because of the lack of knowledge about long-term gender development and sexual function in adults who are affected by syndromes of abnormal sex differentiation.

TABLE 1. Classification of 46,XY Patients With Undermasculinized External Genitalia at Birth, According to Phenotype at Presentation and Diagnosis

Appearance of the External Genitalia in 46,XY Intersex Patients	Cause of Condition
Female external genitalia	CAIS, CGD
Micropenis without hypospadias	Hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, idiopathic
Microphallus with perineoscrotal hypospadias	PAIS, PGD, steroidogenic enzyme defect, Leydig cell hypoplasia, true hermaphroditism, timing defect, multiple congenital anomalies

METHODS

This research was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine (Baltimore, MD). Written, informed consent was obtained from all patients before participation. Participants were asked to complete a written questionnaire and to visit the Johns Hopkins Clinical Research Center to participate in semistructured interviews about their medical/surgical history and to assess their knowledge regarding their clinical condition. Participants were also questioned about their satisfaction with the amount of information they had obtained relating to their condition, as well as their current desire to obtain additional services offered by our clinic. Physical examinations and laboratory tests were conducted, and these results appear elsewhere.[7–9]

Participants

Participants who were recruited for the current study had a 46,XY chromosomal complement and were affected by abnormal sex differentiation that resulted in the following phenotypes at birth: 1) normal female external genitalia, 2) micropenis without hypospadias, or 3) ambiguous external genitalia with perineoscrotal hypospadias. Karyotyping became available to our clinic in 1960; from 1953 to 1960, Barr body analysis was performed.[10,11] Karyotyping was used to confirm the genetic sex of participants when originally based on Barr bodies. All participants were 21 years of age or older and had formerly been treated at the Johns Hopkins Pediatric Endocrine Clinic.

Etiologic Diagnosis

Criteria for Etiologic Diagnosis of 46,XY Participants With Normal Female External Genitalia

Participants with normal female external genitalia consisted of 2 distinct conditions: complete androgen insensitivity syndrome (CAIS) and complete gonadal dysgenesis (CGD). The latter condition is also referred to as Swyer's syndrome.[12]

In the case of CAIS, elements of diagnosis included the presence of testes and spontaneous breast development at puberty when the gonads remained intact but without menses and absent or sparse axillary and pubic hair. These individuals presented with normal to high levels of testosterone and elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[13] An androgen receptor (AR) gene mutation was identified for all of the women who had CAIS in our clinic and participated in this study.[7]

Patients with CGD presented with an absence of breast development and primary amenorrhea at puberty.[13] All of these women in the current study had well-developed müllerian ducts, including a normal uterus and fallopian tubes. In all cases, bilateral streak gonads were removed to prevent malignancy. On administration of estrogen treatment, all women with CGD experienced menses, and 1 successfully carried pregnancies after in vitro fertilization with donated eggs. Some of these women had an SRY gene mutation.[14] CGD can also be attributable to a mutation of 1 of several transcription factors required for the formation of a gonadal anlagen and their differentiation into testes.[15] These factors exert multiple functions; therefore, their mutations result in abnormalities beyond CGD. For example, steroidogenic factor 1 mutations are accompanied by adrenal insufficiency and central nervous system lesions, WT-1 mutations result in the WAGR syndrome, SOX-9 mutations are associated with camptomelic dysplasia, and DAX-1 duplication leads to ambiguous genitalia.[16] None of our patients who had CGD and participated in the present study were affected by these additional malformations.

Criteria for Etiologic Diagnosis of 46,XY Participants With Congenital Micropenis

The specific causes of micropenis included hypogonadotropic hypogonadism (Kallmann's syndrome, panhypopituitarism, various degrees of septo-optic dysplasia), hypergonadotropic hypogonadism, and idiopathic cases.[17] Congenital micropenis, as opposed to a small phallus (or microphallus), refers to a penis with a male-typical urethral opening at the tip. Stretched length of a micropenis at birth was <1.9 cm (2.5 standard deviations below the normal mean) for affected individuals. Causes underlying micropenis of participants for the current study appear elsewhere.[8]

Criteria for Etiologic Diagnosis of 46,XY Participants With Ambiguous External Genitalia Including Perineoscrotal Hypospadias

Participants with ambiguous external genitalia were selected for both a small phallus and perineoscrotal hypospadias. Participants with hypospadias on the shaft or glans of the penis were excluded from the present study. Although the phenotype for ambiguous genitalia was similar for all participants, causes underlying their condition varied. In a number of cases, information was insufficient to establish a definitive diagnosis.

For participants who are affected by partial androgen insensitivity syndrome (PAIS), androgen production was normal with often mildly elevated testosterone and dihydrotestosterone levels and a normal testosterone/dihydrotestosterone ratio during the neonatal period.[18] The presence of a utriculovaginal pouch ending blindly without a uterus was observed. Limited müllerian ducts, usually remnants of fallopian tubes, were observed at laparotomy or laparoscopy in some of the participants with PAIS.

PAIS, like CAIS, is transmitted as an X-linked trait. This type of X-linkage proved helpful in the diagnosis of some participants' conditions. The gold standard for diagnosis of PAIS should be the demonstration of an AR gene mutation. However, such mutations were not identified in some of our patients despite the observation of abnormal AR binding properties (low B_{max} and/or high K_d) in studies of cultured sex skin fibroblasts.[19] Perhaps candidate proteins believed to be important for the biological activity of the AR may be impaired, resulting in partial expression of androgen responsive genes for these participants. Alternatively, it is possible that some participants were affected by 17β-hydroxysteroid dehydrogenase-3 (17β-HSD-3) deficiency, which bears close resemblance to PAIS at initial presentation. This possibility was recently suggested by a study of subjects with genital ambiguity in The Netherlands, in which the incidence of 17β-HSD-3 deficiency was found to be 0.65 times that of AIS.[20]

Partial gonadal dysgenesis (PGD) was defined as an abnormality of the testicular gonads that involved both Leydig and Sertoli cell function. Dual abnormality in the production of testosterone and müllerian inhibiting substance (MIS) results in ambiguous genitalia coupled with incomplete suppression of müllerian duct formation.[21] Individuals who are affected by PGD and participated in this study had a fully or partially formed uterus. In the neonatal period, low levels of androgens and all androgen precursors were evident in affected individuals. Measuring MIS has recently been shown to distinguish successfully between GD and AIS.[22] CGD and PGD are associated with low levels of MIS, whereas CAIS and PAIS are associated with normal to high levels. Unfortunately, because participants in our study came to medical attention 20 or more years ago, measurements for MIS were unavailable. It is probable that PGD, like CGD, results from mutations of transcription factors necessary for early gonad formation.

Numerous additional causes underlying ambiguous genitalia were detected in our study population. Steroidogenic enzyme defect was one, which results from a deficiency of any 1 of the enzymes necessary to produce testosterone or dihydrotestosterone from cholesterol, thus leading to ambiguous external genitalia. This diagnosis required the study of the final androgen products

testosterone and dihydrotestosterone and also of their precursors (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone, 17-hydroxyprogesterone, and androstenedione). A decrease of any of these steroids along with accumulation of precursors indicated abnormal enzymatic activity at a specific point in this biosynthetic pathway. All of the genes involved in this pathway are now known.[23] Studies of gene mutations could confirm the specific biosynthetic abnormality for affected individuals; however, such mutation studies are time-consuming and expensive at this time.

Another cause of ambiguous genitalia was Leydig cell hypoplasia; a decreased number of Leydig cells caused decreased androgen secretion and partial masculinization of the genitalia. It is possible that the low number of Leydig cells in some patients resulted from LH receptor mutations.[13] It would be expected that normal Sertoli cell function was maintained, but this was not always the case and some participants who presented with signs of MIS deficiency similar to PGD.

True hermaphroditism is a condition in which normally functioning follicles develop along with tubules and Leydig cells in the gonads of an individual. The degree of masculinization of the genitalia is related to the number of functioning Leydig cells, whereas the degree of müllerian duct formation is related to the extent of Sertoli cell function. More than half of the participants with true hermaphroditism possess a 46,XX karyotype; approximately 10% are 46,XY or 46,XX/46,XY chimeras, and a few are 45,X0/46,XY mosaics.[24] True hermaphroditism can be determined only by microscopic examination of the gonads and may be a variant of GD.

We have described a condition termed "timing defect."[25] In such cases we postulated that the production of testosterone by the Leydig cells was delayed past the normal fetal onset of masculinization of the external genitalia in males. When masculinization occurred late in fetal life, fusion of the labioscrotal folds and development of a full penile urethra was not possible. At puberty, affected individuals produced and responded to androgens in a male-typical manner.

Abnormalities of sex differentiation can occur in association with multiple congenital anomalies.[26] Among these are the CHARGE syndrome, Vater syndrome, and exstrophy-epispadias complex.

Patient Chart Review

Each patient who was evaluated in the Pediatric Endocrine Clinic had a patient identification card on file that included his or her Johns Hopkins history number, date of birth, last known address, parent contact information, date of initial visit, and address of referring physician. When known, the clinical diagnosis was listed on the patient identification cards. All identification cards in our clinic were examined to determine those patients who were appropriate for recruitment (46,XY with an intersex condition described earlier, 21 years of age or older, and a past patient at the Johns Hopkins University Pediatric Endocrine Clinic). Since Wilkins's initiation of the Johns Hopkins Pediatric Endocrine Clinic, medical charts were kept on the premises for all patients who were examined. Complete medical and surgical charts from the Johns Hopkins Medical Records Department were also reviewed for each patient who consented to study participation.

Techniques Used for Locating Eligible Participants

Eligible participants were located via a variety of tracking methods. First, we checked the active patient lists at Johns Hopkins Hospital to determine whether individuals were currently receiving care at our medical institution. If not listed in the active files, then individuals were located with Internet search engines for a current mailing address, telephone number, and/or e-mail address. For cases in which Internet searches proved unsuccessful, the Motor Vehicle Administration in the state where the patient was known to reside last was contacted.

Once located, patients were mailed an invitation to participate in the study. This letter stated that the purpose of our study was to determine the long-term outcome of former patients who were treated for various endocrine conditions. Former patients, not their parents, were contacted directly because they were adults at the time of study. Individuals were asked to indicate whether they desired to participate, desired more information before deciding to participate, or did not wish to be contacted further. When individuals chose the last option, no additional contact was made, as requested by the Johns Hopkins Joint Committee on Clinical Investigation.

Study Protocol

After the receipt of informed consent, participants were mailed a written questionnaire that asked about their knowledge of their condition. Participants' evaluation of their level of understanding of medical history included knowledge of karyotype, genital ambiguity at birth if relevant, gonadal development, cause of condition, gender reassignment if relevant, genital reconstructive surgeries if relevant, and level of understanding of endocrine treatment in adulthood. To be considered as having good knowledge of their history, participants needed to be informed about all of these aspects of their condition. Participants were also asked about their degree of satisfaction with their amount of knowledge with the following yes/no question: Are you presently satisfied with how much you understand about your medical history? Finally, participants were asked whether they desired additional services from our clinic in the form of 1) talking one-to-one with someone about problems concerning gender and sexuality and/or 2) attending an organized meeting to discuss issues of gender and sexuality for adults with similar endocrine conditions. All participants were asked whether they desired additional education about their particular condition and treatment history. Educational material about normal sex differentiation and the syndromes of abnormal sex differentiation was made available to participants in a semistructured interview by providing them with our web site on syndromes of abnormal sex differentiation (www.hopkinsmedicine.org/pediatricendocrinology/intersex). Finally, contact information for male and female counselors was provided to participants who desired such services.

Participants were given the option of completing the written questionnaire during the course of a telephone conversation. This was then followed by a semistructured interview to verify their original written questionnaire responses or to elaborate on unclear responses during the visit to the Johns Hopkins Clinical Research Center.

Statistical Analysis

Descriptive statistics and the χ^2 test of association were performed. For the χ^2, an $\alpha = 0.95$ was used and $P < .05$ was considered statistically significant.

RESULTS

Sample Selection

Among the 183 eligible patients who were on file in our clinic and are presently 21 years of age or older, 50 (27%) were not located despite multiple searching strategies (Table 2). Patients who were not located did not differ among the 3 genital phenotypes at birth (female, ambiguous, micropenis; $P > .05$) or current gender ($P > .05$). Of the remaining 133 individuals, 37 were unavailable for study because of developmental delay or death (Table 2).

Patients With Developmental Delay

Twenty-one patients (12%) were affected by developmental delay as indicated by their medical chart. These individuals were institutionalized and/or delayed in their development to the extent that communication was limited and thus completion of the questionnaire was not possible. The proportion of patients with delay was highest in the men and women with congenital micropenis ($\chi^2 = 7.72$; $P < .05$).

Developmental delay is known to occur in individuals with congenital micropenis.[17,27] Patients from our clinic with both congenital micropenis and developmental delay were affected by CHARGE syn-

TABLE 2. Reasons for Ineligibility for Study Recruitment

	Diagnostic Category						Total
	CAIS	Micropenis		Ambiguous		CGD	
	(Women)	Women	Men	Women	Men	(Women)	
Total sample	20	12	31	50	64	6	183
Not located	4 (20%)	2 (17%)	8 (26%)	18 (36%)	17 (27%)	1 (17%)	50 (27%)
Developmental delay	0	4 (33%)	7 (23%)	3 (6%)	7 (11%)	0	21 (12%)
Deceased	0	0	1 (3%)	5 (10%)	10 (16%)	0	16 (9%)

drome ($n = 1$), septo-optic dysplasia with variable brain abnormalities ($n = 6$), Prader-Willi syndrome ($n = 1$), Rudd syndrome ($n = 1$), and occipital encephalocele ($n = 2$).

Developmental delay can also be associated with ambiguous genitalia.[28,29] Patients in our clinic with both ambiguous genitalia and developmental delay were affected by Kennedy syndrome ($n = 2$), an unnamed syndrome described by Urban et al[30] ($n = 2$), CHARGE syndrome ($n = 1$), Walker-Warburg syndrome ($n = 1$), cerebral palsy ($n = 1$), septo-optic dysplasia ($n = 1$), and psychomotor delay of unknown origin ($n = 2$). We had no evidence for developmental delay among patients who were born with unambiguously female genitalia.

Deceased Patients

Sixteen patients (9%) were deceased. The proportion of deceased patients was highest in the group of men who were born with ambiguous genitalia ($\chi^2 = 15.9$, $P < .05$). The death of 1 man with congenital micropenis was attributed to cardiac disease. All deaths among women who were born with genital ambiguity were the result of renal disease associated with Wilms tumors ($n = 5$). Deaths among men who were born with genital ambiguity were attributed to renal disease associated with Wilms tumors ($n = 2$), suicide ($n = 2$), lactic acidosis ($n = 1$), adverse reaction to medication ($n = 1$), and unknown cause ($n = 4$).

Patients Who Participated in the Present Study

Seventy-five (78%) of the 96 eligible patients who were located and invited to participate in the study consented to and completed study participation. The remaining 21 individuals (22%) either declined to participate or did not complete their participation in the study after providing informed consent (Table 3). Individuals who chose not to participate did not differ by genital phenotype at birth (female, ambiguous, micropenis; $P > .05$) or current gender ($P > .05$).

Knowledge of Medical/Surgical History

Eighteen (53%) of the 34 men who participated in our follow-up studies exhibited a good understanding of their medical and surgical history, whereas the remaining 16 men (47%) demonstrated a poor understanding (Table 4). Knowledge of medical/surgical history did not differ for men who were born with a micropenis versus those who were born with ambiguous genitalia ($P > .05$).

Twenty-two (54%) of the 41 women who participated in our follow-up studies exhibited a good understanding of their medical/surgical history, whereas 18 women (44%) exhibited knowledge of their genital ambiguity but were unaware of their karyotype or gonadal development. One woman (2%) was uncomfortable with discussing her history; therefore, the extent of her knowledge could not be determined (Table 5). Women who were born with female genitalia (CAIS and CGD) exhibited a poorer understanding of their history than did women who were born with a micropenis or ambiguous genitalia ($\chi^2 = 9.08$; $P < .05$).

Participants did not differ by their current gender regarding knowledge of their medical/surgical history ($P > .05$). It is impossible to know whether patients who were poorly informed about their condition were never provided with this knowledge or this information was provided but then forgotten or denied.

Satisfaction With Knowledge Received About Medical/Surgical History

Thirteen men (38%) were satisfied with their knowledge of their medical/surgical history. Satisfaction did not differ for men according to their genital appearance (ambiguous or micropenis) at birth ($P > .05$). Seventeen men (50%) were dissatis-

TABLE 3. Description of Intersex Patients Who Were on File at the Johns Hopkins Pediatric Endocrine Clinic and Were Available for Study Recruitment

	Diagnostic Category						Total
	CAIS	Micropenis		Ambiguous		CGD	
	(Women)	Women	Men	Women	Men	(Women)	
Available for recruitment	16	6	15	24	30	5	96
Participated	14 (88%)	5 (83%)	13 (87%)	18 (75%)	21 (70%)	4 (80%)	75 (78%)
Refused to participate	2 (12%)	1 (17%)	2 (13%)	6 (25%)	9 (30%)	1 (20%)	21 (22%)

TABLE 4. Knowledge of Medical and Surgical History of Johns Hopkins University Pediatric Endocrine Patients Who Were Raised Male (Parent/Physician Assigned) and Participated in Our Follow-up Studies

	Diagnostic Category		Total
	Micropenis	Ambiguous	
Good knowledge	8 (62%)	10 (48%)	18 (53%)
Poor knowledge	5 (38%)	11 (52%)	16 (47%)
Undetermined knowledge	0	0	0
Total	13	21	34

fied with their understanding of their condition, and 4 men (12%) did not respond to this question.

Among men who were satisfied with their knowledge, 10 (77%) were considered to have good knowledge of their medical/surgical history and 3 (23%) exhibited poor knowledge of their history. Among men who were dissatisfied with their knowledge, 5 (29%) were well informed and 12 (71%) were not (Table 6).

Twenty-seven women (66%) were satisfied with their knowledge of their medical/surgical history. Satisfaction did not differ for women according to their genital appearance (female, ambiguous, micropenis) at birth ($P > .05$). Twelve women (29%) were dissatisfied with their understanding of their condition, and 2 women (5%) did not respond to this question.

Among 27 women who were satisfied with their knowledge, 17 (63%) were considered to have good knowledge of their medical/surgical history and 10 (37%) exhibited poor knowledge of their history. Among 12 women who were dissatisfied with their knowledge, 5 (42%) were well informed about their condition and 7 (58%) were not (Table 6).

Participants differed by sex of rearing regarding their satisfaction with knowledge of their medical/surgical history ($\chi^2 = 4.55$; $P < .05$), with more women than men reporting satisfaction. In addition, amount of knowledge corresponded to satisfaction for men ($\chi^2 = 6.6$; $P < .05$) but not for women ($P > .05$). Men with greater knowledge reported more satisfaction with that knowledge. However, no such relationship was observed for women.

Desire for Additional Services

Some of the men reported a desire for additional services, such as speaking to a person one-to-one (47%) and attending a meeting with other individuals who are affected by syndromes of abnormal sex differentiation to discuss gender issues (26%). Similarly, some of the women reported a desire to talk one-to-one (44%) and attend a meeting (39%). The desire for additional services did not differ for participants according to their current gender ($P > .05$).

DISCUSSION

Limitations of Etiologic Diagnosis

One of the major limitations encountered in our study was the inability to make an etiologic diagnosis for all patients. This problem was unique to patients with ambiguous genitalia. Patients who were classified as having PAIS on the basis of studies of sex skin fibroblasts had no identifiable AR gene mutation. These same individuals also did not have 1 of the 4 most common mutations of the 17β-HSD-3 gene.[20]

It was less difficult to classify patients with ambiguous genitalia into the PGD category as patients who present with well-developed müllerian ducts fit this diagnosis. In the area of abnormal steroid biosynthetic pathways, patients' conditions were diagnosed on the basis of steroid studies at the appropriate time of life (before 4 months of age or at puberty when the gonads remained intact).

Genitalia as a Bioassay for Androgen Action

It is widely accepted that masculinization of the genitalia requires adequate effects of androgens. A simple corollary is that the degree of undermasculinization will be proportional to the degree of deficiency of androgen effects. This is true regardless of cause (failure to produce androgens or failure to respond to androgens).

We can conclude that regardless of whether fetal exposure to androgens masculinizes the human central nervous system, patients with undermasculinized genitalia were exposed to androgen effects below the normal male range. Thus, regardless of whether this is important to psychosexual development, degree of decreased prenatal androgen exposure can be assessed by the appearance of the genitalia at birth. On this principle, we believe that whatever the cause of genital ambiguity in a 46,XY patients, the most feminized patients would benefit from female sex of rearing and the most masculinized patients would optimally respond to male sex of rearing. In addition, our follow-up studies have shown that the number and difficulty of surgical

TABLE 5. Knowledge of Medical and Surgical History of Johns Hopkins University Pediatric Endocrine Patients Who Were Raised Female (Parent/Physician Assigned) and Participated in Our Follow-up Studies

	Diagnostic Category				Total
	CAIS	Micropenis	Ambiguous	CGD	
Good knowledge	5 (36%)	4 (80%)	13 (72%)	0	22 (54%)
Poor knowledge	9 (64%)	1 (20%)	5 (28%)	3 (75%)	18 (44%)
Unknown knowledge	0	0	0	1 (25%)	1 (2%)
Total	14	5	18	4	41

TABLE 6. Self-Reported Degree of Satisfaction by Participants Who Are Currently Living as Men or Women Concerning Level of Understanding of Their Medical/Surgical History

	Level of Knowledge							
	Good		Poor		Unknown		Total	
	Men	Women	Men	Women	Men	Women	Men	Women
Satisfied	10 (55%)	17 (77%)	3 (19%)	10 (56%)	0 (0%)	0 (0%)	13 (38%)	27 (66%)
Dissatisfied	5 (28%)	5 (23%)	12 (75%)	7 (38%)	0 (0%)	0 (0%)	17 (50%)	12 (29%)
Unknown	3 (17%)	0 (0%)	1 (6%)	1 (6%)	0 (0%)	1 (100%)	4 (12%)	2 (5%)
Total	18 (100%)	22 (100%)	16 (100%)	18 (100%)	0 (0%)	1 (100%)	34 (100%)	41 (100%)

procedures necessary for either sex of rearing should be discussed when assigning gender.[8]

Reproduction

Among 46,XY intersex patients, the only conditions with potential for fertility are 5α-reductase deficiency and timing defect.[31] In cases of CGD and PGD, there exists the potential for in vitro fertilization in patients who are reared female.

Intersex and Transsexualism

In retrospective follow-up studies of self-defined patient samples, it is possible to recruit accidentally patients who are postoperative transsexuals. Because of this potential confound, we included in our studies only patients whose conditions were diagnosed and treated in the Johns Hopkins University Pediatric Endocrine Clinic.

Patients Not Located

Fifty individuals (27%) were not located, and failure to locate these patients may be attributed to the length of time since they were last seen at Johns Hopkins. The tendency of people to relocate for education and work opportunities is well established in our society; therefore, it is not surprising that 27% of the original group of patients spanning a period of 50 years were not located. Patients who were not located did not cluster according to age. Before study initiation, we had anticipated greater difficulty in finding patients who were reared female because of their likelihood for name change on marriage. This was not the case, however, as our ability to contact patients did not differ according to their current gender.

Developmental Delay

The incidence of developmental delay was highest for individuals who were born with a micropenis followed by those who were born with ambiguous genitalia, and this observation is consistent with previous reports.[27–29] Somewhat surprising was the number of patients who had profound developmental delay and were assigned to the female gender. As this group seems to have obstacles far greater than a small phallus for sexual intercourse, this decision seems questionable. However, for some of these patients, the extent of developmental delay may not have been evident until after a female gender assignment had been made.

Deaths

The incidence of death was highest among patients who were born with ambiguous external genitalia, and several of these deaths were attributed to Wilms tumors known to be malignant. It is difficult to determine the relationship between suicide and endocrine condition in the 2 men for whom this information is known, as these deaths occurred before study initiation. Considering the enormous impact that having ambiguous genitalia exerts on patients, it is possible that their intersex conditions contributed to the suicide of these men.

Refusal to Participate

Among the patients who were eligible for study participation, 78% participated in all aspects of the study. Among the 21 patients who did not participate, 3 had consented to study participation but never returned a completed questionnaire or completed a physical examination. We had anticipated greater nonparticipation rates from women because of their desire for confidentiality regarding their karyotype. This was not the case, and nonparticipants did not differ according to current gender or phenotype at birth. It is unfortunate that we were unable to determine the reason for refusal of these patients. As previously noted, our research protocol did not permit us to contact individuals who chose not to participate.

Knowledge of Medical/Surgical History

Approximately half of the patients who participated demonstrated a good knowledge of their history, and this knowledge did not differ according to their sex of rearing. Patients who were born with ambiguous genitalia or micropenis and were reared female exhibited better knowledge than those who were born with normal female genitalia. We speculate that because women with CAIS and CGD had a totally female phenotype, they required no or few surgical procedures, thus leading to fewer opportunities to be informed of their condition. In addition, these patients may not have requested as much information as the women with ambiguous genitalia. Slijper et al[6] also reported a poor understanding of diagnosis among 46,XY patients who were reared female. Their results may be attributable to the fact that many patients were affected by CAIS and thus had female genitalia. Our study indicates that attempts to improve knowledge of their condition among intersex patients needs to focus on patients

with female genitalia (CAIS and CGD) as well as those with ambiguous genitalia or a micropenis.

Satisfaction With Knowledge

More women (66%) than men (38%) were satisfied with how well they understood their medical/surgical history. Cancer patient dissatisfaction with their medical information has been attributed to limited time for discussion, poor communication skills of medical staff, medical staff's withholding information, and patient inability to remember information.[32] It is reasonable to suspect that similar reasons contributed to the dissatisfaction reported by intersex patients in the present study. Resources designed to increase satisfaction with the amount of medical information provided to intersex patients would greatly serve this population. Unfortunately, information provided to the patients through media such as the Internet is currently unregulated and can be misleading.[33]

For men but not for women, satisfaction with knowledge related to the patients' understanding of their history. Observations of patients with other disorders reveal that some individuals prefer to know only partial information concerning their condition, whereas others wish to know as many details as possible.[34] Women in the present study were more likely than men to be satisfied with what the authors considered to be poor medical/surgical knowledge. One interpretation is that some of these women had a better understanding of their condition than they indicated but were unwilling to discuss their diagnosis openly because of concerns about confidentiality. In all of our dealings with patients for follow-up studies, confidentiality was extremely important to patients.

Additional Services

Roughly half of the men and women who participated desired additional services for discussing issues of gender and sexuality. This observation, taken with the fact that some patients were dissatisfied with the knowledge provided to them concerning their condition, illustrates the importance of offering education and counseling to patients and their families. Although the present data identify groups of patients for whom education would prove useful, the practical questions of what information to provide and when to provide it remain unresolved.

Future Studies

In addition to offering guidelines for educating patients and their families, future studies of intersex patients could include information about the impact of family members and friends on psychosexual development in individuals who are affected by syndromes of abnormal sex differentiation. For example, the degree of parents' understanding of their child's intersex condition may have a major impact on later medical knowledge and satisfaction with treatment by patients. In addition, if parents of children with intersex conditions are themselves at an increased risk for hardships such as divorce or substance abuse, then this could translate into psychosexual difficulties for patients. We are currently in the process of collecting such data from parents of intersex patients.

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