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Gender Dysphoria and Gender Change in Androgen Insensitivity or Micropenis

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This review article answers three questions relevant to the medical management and care of individuals born with complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), or a micropenis: (1) Do any of these individuals reassign themselves from their initial gender assignment? (2) Do more reassign than the ones who do not? (3) Is there evidence of gender dysphoria in those who do not self-initiate reassignment? Reviewed were all articles on CAIS, PAIS, and micropenis cited in K. J. Zucker (1999) plus articles published through 2004. There were no documented cases of gender change in individuals with CAIS ($N = 156$ females) or micropenis ($N = 89$: 79 males, 10 females). Nine (9.1%) out of 99 individuals with PAIS changed gender. Thus, self-initiated gender reassignment was rare. Gender dysphoria also appears to be a rare occurrence. The best predictor of adult gender identity in CAIS, PAIS, and micropenis is initial gender assignment.

KEY WORDS: complete androgen insensitivity syndrome; partial androgen insensitivity syndrome; androgen resistance syndromes; micropenis; gender identity; gender dysphoria.

INTRODUCTION

The traditional medical management of intersex infants has recently been challenged, especially in 46,XY infants assigned and reared female. The question of whether or not such gender assignment is appropriate and in the best interest of the child has been raised. To help answer this challenge, it is important to conduct long-term follow-up studies of such infants to ascertain whether or not they have established and maintained a gender identity commensurate with their initial gender assignment or show evidence of gender dysphoria and gender change. The purpose of this article is to review and summarize currently available data on gender outcome in 46,XY individuals with partial or complete androgen insensitivity or with the condition of micropenis.

Androgen insensitivity is an X-linked disorder of genetic male differentiation that is the result of an absent or defective androgen receptor (AR) gene. In this syndrome, the fetal testes function normally, but the utilization of androgens is impaired. The extreme variant of this condition is complete androgen insensitivity syndrome (CAIS). All 46,XY individuals with CAIS present with female-typical external genitalia. Internally, there are no Mullerian structures, such as a uterus or proximal vagina, due to the effects of the anti-Mullerian hormone secreted by the testes (along with testosterone and estradiol). In some cases, rudimentary Wolffian or male internal structures, epididymis and vas deferens, are present. Recently, residual activity of mutant AR-genes have been found to explain such internal male development. Hannema et al. (2004) suggest that individuals having any Wolffian development be classified as "severe" rather than as complete androgen insensitive. The distal vagina is usually short, dimple-like, with a blind ending. Infants with CAIS are always announced and reared as girls. The diagnosis is usually not made at birth. If the testes are not removed before puberty, their (normal) estradiol production will result in development of breasts. The testes must eventually be removed due to the risk of cancer and, after removal, life-long estrogen replacement therapy is started in adolescence. Because of the lack of a uterus, CAIS individuals are amenorrheic, and the androgen insensitivity leads to sparse or absent body, axillary, and pubic hair.

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If the genetic defect does not cause a complete block of the androgen receptor, a partial androgen insensitivity syndrome (PAIS) results, leading to variable hypoandrogenization and imperfect masculinization, despite normal androgen production. Presentation of the external genitalia is highly variable and can range from a penis with perineoscrotal hypospadias, with or without cryptorchidism, to a micropenis, with or without hypoplastic labioscrotal swellings, which may or may not be completely fused to form a scrotum. Remnants of female (Mullerian) internal reproductive structures have been found in some individuals diagnosed with PAIS. Infants with PAIS are assigned to either the male or female gender, depending to some extent on the degree of hypomasculinization. Virilization at puberty will also be variably incomplete.

The term micropenis denotes a completely differentiated penis with the urethral meatus at the tip and very small size. It is used as a clinical diagnostic term if the following criteria are met: (1) 46,XY karyotype, (2) testes, descended or undescended, (3) urethral meatus at the tip of the glans penis, i.e., no hypospadias, (4) stretched penile length (from pubic ramus to the tip of the glans) at or below 2.5 *SD* for age and stage of puberty (see Table I in Lee et al., 1980). Lee et al. also describe a procedure to measure the penis and provide standards of penile length from 30 weeks of age through adulthood. Accordingly, in a 46,XY newborn, micropenis denotes a penis $\leq$1.9 cm stretched length; in the adult, $\leq$9.3 cm. 46,XY newborns with micropenis have been assigned to either the female or male gender, depending largely on the locally prevailing policy of medical management. Micropenis can occur in isolation or be associated with a variety of intersex syndromes.

The gender outcomes of principal interest in this article are (1) gender identity and (2) gender dysphoria. Gender identity refers to the basic sense of being a boy or girl, man or woman (Money & Ehrhardt, 1972). Dysphoria denotes a state of dissatisfaction, anxiety, restlessness or fidgeting (Random House College Dictionary, 1988). For the purpose of this article, gender dysphoria is defined as a feeling of dissatisfaction or anxiety about oneself as male or female or dissatisfaction with one's assigned or legal gender.

METHOD

For the purpose of this paper, I reviewed all articles on CAIS, PAIS, and micropenis cited by Zucker (1999), along with additional articles found via computer search of Medline, PsycINFO, and Cumulative Index to Nursing and Allied Health up to and including the year 2004. The search terms were male pseudohermaphroditism, androgen insensitivity syndromes, complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), micropenis, intersex, ambiguous genitalia, microphallus, gender identity, gender dysphoria, and gender change.

Inclusion criteria for CAIS cases were the following: (1) identification of the AR gene mutation and/or a set of clinical criteria including (2) normal female-appearing external genitalia, (3) testes, (4) 46,XY karyotype, (5) no menses, (6) sparse or absent virilization, and (7) normal or high levels of testosterone. For PAIS, the ideal selection criterion would also be documentation of a defective androgen receptor gene, which constitutes the "gold standard" for the diagnosis (Migeon et al., 2002a). However, it is generally well known that it is difficult to demonstrate the presence of such a mutation in many cases. For instance, Migeon et al. (2002b) could demonstrate the presence of an AR-gene mutation in only 6 of 14 individuals classified as PAIS, despite abnormal AR-binding properties in cultured sex skin fibroblasts. For this reason, selection criteria for those with PAIS were either (1) presence of an AR-gene mutation and/or (2) endocrine findings and description of external genitalia that conventionally would permit the diagnosis of PAIS. The selection criteria for individuals with a micropenis are the clinical criteria defined earlier. The report by Reilly and Woodhouse (1989) was excluded because it did not meet these criteria. Only articles that clearly indicated the number of patients identified and their ages were utilized. The articles by Hinman (1972) and Slijper, Drop, Molenaar, and Keizer-Schrama (1998) were excluded because this criterion was not met. In addition, the case selection was based on information within the articles that allowed a reasonable judgment about the status of an individual's current gender identity and/or social gender and his/her history of self-initiated gender change. These criteria were not met by Money, Mazur, Abrams, and Norman (1981) where all individuals were infants, and Dessouky (2003), who noted gender change from female to male in 14 individuals with a diagnosis of PAIS, but in abstract form only.

RESULTS

Complete Androgen Insensitivity Syndrome

Table I summarizes the reports that met the inclusion criteria. They include a total of 156 individuals. The AR-gene mutation was found in 62 cases, all of which came

Table I. Gender Development in 46,XY Individuals Born with Complete Androgen Insensitivity Syndrome

General information				Gender history					Latest report			
Reference	Country	Androgen receptor detected	*n*	Neonatal gender assignment	Physician imposed gender reassignment	Age at physician imposed gender reassignment	Patient initiated gender reassignment	Age at patient initiated gender reassignment	Age at time of study (years)	Lives as (M, F, other)	Identifies as (M, F, other)	Gender dysphoric (yes, no, NI)
Morris and Mahesh (1963)	USA	NI	3	F	—	—	—	—	18, 18, 21	F	F	No
Teter and Boczkowski (1966)	Poland	NI	4	F	—	—	—	—	18–27	F	F	No
Masica, Money, and Ehrhardt (1971)[a]	USA	NI	10	F	—	—	—	—	17–34	F	F	No
Imperato-McGuinley, Pichardo, Gautier, Voyer, and Bryden (1991)	Dominican Republic	NI	10	NI	—	—	—	—	18–76	F	F	No
Slob et al. (1993)	Netherlands	NI	4	F	—	—	—	—	19, 20, 49, 63	F	F	No
Costa et al. (1997)	Brazil	NI	2	F	—	—	—	—	14, 18	F	F	No
Slijper et al. (2000)	Netherlands											
Children		NI	15	F	—	—	—	—	NI	F	NI	NI
Adults		10	10	F	—	—	—	—	24.11–70	F	F	No
Wisniewski et al. (2000)	USA	14	9[b]	F	—	—	—	—	25–65	F	F	No
Hines et al. (2003)	UK											
Volunteers		NI	12	F	—	—	—	—	>15	F	F	No
Medical chart		10	10	F	—	—	—	—	>15	F	F	No
Melo et al. (2003)	Brazil		11									
Case 1		P904V		F	—	—	—	—	5.8	F	F	No
Case 2		S119X		F	—	—	—	—	9.5	F	F	No
Case 3		R779W		F	—	—	—	—	14	F	F	No
Case 4		R752X		F	—	—	—	—	14.5	F	F	No
Case 5		R855C		F	—	—	—	—	16	F	F	No
Case 6		M807V		F	—	—	—	—	16	F	F	No
Case 7		R855C		F	—	—	—	—	17	F	F	No
Case 8		N705S		F	—	—	—	—	19	F	F	No
Case 9		L768V		F	—	—	—	—	19.8	F	F	No
Case 10		N705S		F	—	—	—	—	34	F	F	No
Case 11		L768V		F					43	F	F	No
Hooper et al. (2004)	Brazil	17	17	F	—	—	—	—	5 were <18 12 were 18–74	F	F	No
Diamond and Watson (2004)	UK/USA	NI	39	F	—	—	—	—	NI	F	F	No
Total			156[c]					0				0

Note. NI: no information.

[a] Same subjects as Money, Ehrhardt, and Masica (1968).

[b] Five subjects not counted, previously reported on in Masica et al. (1971).

[c] 128 individuals 18 years and older, 28 individuals 0–18 years.

from the most recently published studies (Hines, Ahmed, & Hughes, 2003; Hooper et al., 2004; Melo et al., 2003; Slijper, Frets, Boehmer, Drop, & Niermeijer, 2000; Wisniewski et al., 2000). None of these individuals initiated a gender reassignment to male. Most of the articles did not contain any information on gender dysphoria or atypical gender roles as defined by Zucker (1999, p. 7).

Partial Androgen Insensitivity Syndrome

Table II summarizes data on 99 individuals diagnosed with PAIS, in whom 26 were found to have the AR-gene defect. Table II also shows that nine individuals with PAIS changed gender later in life of their own initiative. One was initially assigned male, but 5 days later the assignment was changed to female (Gooren & Cohen-Kettenis, 1991). This person reassigned herself to the male gender at age 30. The initial gender assignment of the second one was female, but was changed to male at 3 weeks (Minto, Liao, Woodhouse, Ransley, & Creighton, 2003). Masculinization was incomplete and, "although still legally a male" (p. 1255), the patient underwent feminizing genital surgery at age 30 and since then "lives as a woman" (p. 1255). The third person initiated reassignment from male to female at age 22 (Migeon et al., 2002b). Diamond and Watson (2004) reported the remaining six, two of whom changed from female to male and four changed from male to female. Two of these latter four were initially assigned as female but changed by a physician to male at ages 18 months and 3 months, respectively, when testes were palpated.

Gender dysphoria without complete gender change was also reported. Money and Ogunro (1974) reported on one individual who was reared as a "hermaphrodite girl" (p. 181). According to Money and Ogunro, this woman had thoughts or fantasies of "a woman haunted by phobic, obsessional doubt that other people, a sexual partner in particular, would easily divine her secret, namely that she was imperfect, an abnormal man/woman, so to speak" (p. 189). Interestingly, this woman had three siblings with the same condition (not available for study), two of whom were known to have changed to live as men.

Micropenis

Table III summarizes the data on 89 individuals with a micropenis, 10 of whom were assigned and reared female. None of these 89 individuals were reported to have changed gender, regardless of whether the original assignment was as a boy or as a girl. Wisniewski et al. (2001) reported that only one male out of 13 was dissatisfied with his gender of rearing and doubted his gender, i.e., showed gender dysphoria, although about half of these persons said they were dissatisfied with their genitals and one man refused to answer questions about his sexual functioning and body image. However, while all five individuals reared female were currently satisfied with their gender identity, four (80%) of them said that at some point they had questioned their gender of rearing. Those reared male ($n = 13$) reported being more masculine than those reared female ($n = 5$) and the reverse held true for self-rated femininity. In the most detailed case report available on a male with micropenis, Money (1984b) documented the history of gender change ideation for a period of time in this person's life who, however, never put his fantasies into action.

DISCUSSION

Nine summary statements are justified based upon the findings of this review: (1) Gender identity as female was established and maintained in all individuals diagnosed with CAIS. (2) The majority of individuals diagnosed as PAIS and all of those born with a micropenis maintained their initially assigned gender, whether male or female. (3) Gender change occurred only in PAIS and (4) both from male to female and from female to male. (5) A specific AR-gene mutation was not demonstrated in every individual classified as PAIS or CAIS. (6) AR-gene mutations were documented in PAIS individuals regardless of the gender they developed. (7) AR-gene mutations were also documented in PAIS individuals who changed gender as well as those who did not. (8) No one with CAIS was described as gender dysphoric, although some individuals reported dissatisfaction with various genital and non-genital aspects of their body. (9) One individual with the diagnosis of PAIS and two males with a micropenis clearly demonstrated gender ambiguity, but none initiated a gender change even though one individual with a micropenis had a period of transsexual fantasies, and the other directly expressed dissatisfaction with his gender of rearing.

Three questions posed at the outset of this review can now be answered. Do any individuals with a diagnosis of CAIS, PAIS, or presentation of a micropenis at birth change from their initial gender assignment? Self-initiated gender change is documented for persons diagnosed with only PAIS, not individuals with CAIS or micropenis. The second question asked about frequency of gender change. It is rare even in individuals with PAIS to change gender. Those who do are not the majority of individuals with this

Table II. Gender Development in 46,XY Individuals Born with Partial Androgen Insensitivity Syndrome

General information				Gender history					Latest report			
Reference	Country	Androgen receptor detected	*n*	Neonatal gender assignment	Physician imposed gender reassignment	Age at physician imposed gender reassignment	Patient initiated gender reassignment	Age at patient initiated gender reassignment	Age at time of study (years)	Lives as (M, F, other)	Identifies as (M, F, other)	Gender dysphoric (yes, no, NI)
Morris and Mahesh (1963)	USA	NI	1	F	—	—	—	—	19	F	F	No
Teter and Boczkowski (1966)	Poland	NI	3	F	—	—	—	—	21, 21, 22	F	F	No
Money and Ogunro (1974)	USA	NI							13.5–39			
Group 1			2	F	—	—	—	—		F	F	Yes (1)
Group 2			8	M	—	—	—	—		M	M	No
Madden, Walsh, MacDonald, and Wilson (1975)	USA	NI	1	F	—	—	—	—	28	F	F	No
Assael, Lancet, and Shani (1976)	Israel	NI	1	F	—	—	—	—	40	F	F	No
Beheshti, Hardy, Churchill, and Daneman (1983)	Canada	NI							0.5–27			
Group 1			5	F	—	—	—	—		F	F	No
Group 2			12	M	—	—	—	—		M	M	No
Gooren and Cohen-Kettenis (1991)	Netherlands	1	1	F	—	—	M	30 years	33	M	M	No
Costa et al. (1997)	Brazil	NI	6	M	F	5 days	—	—	15–30	F	F	No
Migeon et al. (2002b)	USA	6	14									
Case 1				M	—	—	—	—	35–39	M	M	No
Case 2				M	—	—	—	—	20–24	M	M	No
Case 3				M	—	—	—	—	25–29	M	M	No
Case 4				M	—	—	—	—	45–49	M	M	No
Case 5				M	—	—	—	—	40–44	M	M	No
Case 6				—	—	—	—	—	35–39	F	F	No
Case 7				F	—	—	—	—	25–29	F	F	No
Case 8				—	—	—	—	—	30–34	F	F	No
Case 9				—	—	—	—	—	20–24	F	F	No
Case 10				F	—	—	—	—	20–24	F	F	No
Case 11				F	—	—	—	—	40–44	F	F	No
Case 12				F	—	—	—	—	35–39	F	F	No
Case 13				F	—	—	—	—	25–29	F	F	No
Case 14				M	M	—	F	22 years	45–49	F	F	No
Melo et al. (2003)	Brazil		14									
Case 1		R855H		M	F	1 year	—	—	1	F	F	No
Case 2		I898F		F	—	—	—	—	14	F	F	No
Case 3		I898F		F	—	—	—	—	18	F	F	No
Case 4		I898F		F	—	—	—	—	19	F	F	No
Case 5		I898F		F	—	—	—	—	20	F	F	No
Case 6		M742V		F	—	—	—	—	30	F	F	No
Case 7		W741C		M	—	—	—	—	2.5	M	M	No
Case 8		R855H		M	—	—	—	—	2.6	M	M	No
Case 9		T602P		M	—	—	—	—	7.3	M	M	No
Case 10		R840S		M	—	—	—	—	7.8	M	M	No

Table II. Continued

General information				Gender history					Latest report			
Reference	Country	Androgen receptor detected	*n*	Neonatal gender assignment	Physician imposed gender reassignment	Age at physician imposed gender reassignment	Patient initiated gender reassignment	Age at patient initiated gender reassignment	Age at time of study (years)	Lives as (M, F, other)	Identifies as (M, F, other)	Gender dysphoric (yes, no, NI)
Case 11		R855H		M	—	—	—	—	13.8	M	M	No
Case 12		T602P		M	—	—	—	—	16	M	M	No
Case 13		R840S		M	—	—	—	—	16.5	M	M	No
Case 14		Y763C		M	—	—	—	—	25	M	M	No
Minto et al. (2003)	UK	NI	9						18–70			
Case 1				F	M	3 weeks	F	30 years	—	F	F	No
Case 2				F	—	—	—	—	—	F	F	No
Case 3				F	—	—	—	—	—	F	F	No
Case 4				F	—	—	—	—	—	F	F	No
Case 5				F	—	—	—	—	—	F	F	No
Case 6				F	—	—	—	—	—	F	F	No
Case 7				F	—	—	—	—	—	F	F	No
Case 8				F	—	—	—	—	—	F	F	No
Case 9				F	—	—	—	—	—	F	F	No
Mazur et al. (2004)	USA	NI	3									
Case 1				M	F	.5 months	—	—	33	F	F	No
Case 2				M	F	18 months	—	—	33	F	F	No
Case 3				M	F	1.5 months	—	—	31	F	F	No
Diamond and Watson (2004)	UK/USA	5[a]	19									
Case 1				M			F	46 years		F	F	No
Case 2				M			F	NI		F	F	No
Case 3				M						M	M	No
Case 4				F						F	F	No
Case 5				F	M	6 years				M	M	No
Case 6				F	M	5 years				M	M	No
Case 7				F	M	1.5 years	F	34 years		F	F	No
Case 8				F	M	2 weeks				M	M	No
Case 9				F			M	18 years		M	M	No
Case 10				F			M	30 years		M	M	No
Case 11				F						F	F	No
Case 12				F						F	F	No
Case 13				F						F	F	No
Case 14				F						F	F	No
Case 15				F						F	F	No
Case 16				F						F	F	No
Case 17				F						F	F	No
Case 18				F						F	F	No
Case 19[b]				F	M	3 months	F	22 years		F	F	No
Total			99[c]				9					1

Note: NI: no information.

[a] Authors refer to another article for the specific DNA conformation.

[b] Additional case from p. 628 of article.

[c] 81 individuals were 18 years and older, 17 individuals were 0–18 years.

Table III. Gender Development in 46,XY Individual Born with Micropenis

General information			Gender history					Latest report			
Reference	Country	*n*	Neonatal gender assignment	Physician imposed gender reassignment	Age at physician imposed gender reassignment	Patient initiated gender reassignment	Age at patient initiated gender reassignment	Age at time of study (years)	Lives as (M, F, other)	Identifies as (M, F, other)	Gender dysphoric (yes, no, NI)
Money and Mazur (1977)	USA	1	M	—	—	—	—	9	M	M	No
Burstein, Grumbach, and Kaplan (1979)	USA	14	M	—	—	—	—	1wk-11.1	M	M	NI
Money (1984a)	USA	1	M	F	3 weeks	—	—	17	F	F	No
Money (1984b)	USA	1	M	—	—	—	—	28	M	M	Yes
Money and Norman (1988)	USA	4									
Case 1			M	F	6 weeks	—	—	18.0	F	F	NI
Case 2			M	F	6 weeks	—	—	10.6	F	F	NI
Case 3			M	F	21 days	—	—	11.2	F	F	NI
Case 4			M	F	9 days	—	—	13.1	F	F	NI
Bin-Abbas, Conte, Grumbach, and Kaplan (1999)	USA							18–27			
Group 1 0–2 years		4	M	—	—	—	—	4 months–2 at start of Testosterone Rx	M	M	No
Group 2 6–13 years		4	M	—	—	—	—	6–13 at start of Testosterone Rx	M	M	No
Wisniewski et al.[e] (2001)	USA										
Group 1		13						21–54			
Case 1			M	—	—	—	—		M	M	Yes
Case 2			M	—	—	—	—		M	M	No
Case 3			M	—	—	—	—		M	M	No
Case 4			M	—	—	—	—		M	M	No
Case 5			M	—	—	—	—		M	M	No

Table III. Continued

General information			Gender history					Latest report			
Reference	Country	*n*	Neonatal gender assignment	Physician imposed gender reassignment	Age at physician imposed gender reassignment	Patient initiated gender reassignment	Age at patient initiated gender reassignment	Age at time of study (years)	Lives as (M, F, other)	Identifies as (M, F, other)	Gender dysphoric (yes, no, NI)
Case 6			M	—	—	—	—		M	M	No
Case 7			M	—	—	—	—		M	M	No
Case 8			M	—	—	—	—		M	M	No
Case 9			M	—	—	—	—		M	M	No
Case 10			M	—	—	—	—		M	M	No
Case 11			M	—	—	—	—		M	M	No
Case 12			M	—	—	—	—		M	M	No
Case 13			M						M	M	No
Group 2		5						23–29			
Case 1			M	F	1.3	—	—		F	F	No
Case 2			M	F	3.3	—	—		F	F	No
Case 3			M	F	1.10	—	—		F	F	No
Case 4			M	F	1.6	—	—		F	F	No
Case 5			M	F	1.6	—	—		F	F	No
Husmann (2004)	USA	20	M	—	—	—	—	18–30	M	M	No
Lee and Houk (2004)	USA	22	M	—	—	—	—	18–32	M	M	No
Total		89[b]				0					2

Note. NI: no information.

[a]Four subjects in study were previously reported on in Money, Lehne, and Pierre-Jerome (1985).

[b]71 adults, 18 children.

diagnosis. Consequently, gender change is the exception to the main finding of this review: the best predictor of gender identity outcome in adulthood is the initial gender assignment. The third question asked whether or not gender dysphoria was present in individuals who did not change gender. Here, the answer is less clear. While it appears that gender dysphoria was present in some individuals, the degree to which it was present (i.e., dissatisfaction with one or two body parts versus many, or just expressed as a global gender dysphoria), as well as its intensity or strength, were not well defined nor systematically studied in the extant reports.

The studies reviewed herein have a number of limitations. (1) Accuracy of diagnosis is sometimes questionable, especially in those cases of PAIS where no AR-gene mutation is found because PAIS in its clinical presentation can closely mimic other intersex conditions. (2) Thorough description with measurements of the appearance of the neonate's genitalia are virtually lacking in all studies reviewed. (3) The use of support groups to select participants also raises a problem of diagnosis, as noted by Hines et al. (2003). Diamond and Watson's (2004) entire sample consisted of individuals from support groups and volunteers who "had confirming diagnosis of the CAIS or PAIS form of the condition" (p. 625). Diamond and Watson provided no medical or endocrinologic information. Accuracy of diagnosis is most important if one wants to make predictions concerning ultimate gender identity outcome that are based on specific syndromes defined by endocrine and/or genetic criteria. This, of course, assumes that accurate medical diagnosis predicts such ultimate outcome. This assumption has yet to be validated, with the possible exception of CAIS. Another limitation of support-group samples is selection bias because individuals self select to join a group and are therefore not representative of the total population under study. (4) Sample sizes were small. This especially applies to the subgroup of female-assigned individuals with micropenis ($n = 10$). Furthermore, there were only six in this subgroup of individuals reared female who were 18 years and older. The oldest was 29 years old. The young ages of this very small group of females are problematic in establishing final adult gender identity outcome with a high degree of confidence because it is known that some intersex individuals and some non-intersex transsexuals change gender in mid-life or later. Thus, expansion of the micropenis database for those assigned and reared female and a longer follow-up period are vital to confirming or challenging the current evidence. (5) Sample follow-ups were often incomplete because of participant refusal or investigators' inability to locate people. (6) In some outcome studies, the investigators were the same individuals as those who provided treatment. A principle of clinical research is the separation of clinical service from outcome assessment. Participants may report findings to please the service provider, and the provider may minimize negative or adverse findings. (7) A final limitation is assessment methodology. Assessment of both gender identity and gender dysphoria in most studies was by unstructured self-reports of the individuals investigated. This appeared to be especially true when evaluating the presence or absence of gender dysphoria in those who did not change gender. Consequently, judgments about gender dysphoria were based on self-report and impressions of the investigators. An improvement in future studies would be incorporation of measures that appreciate the multidimensional nature of both gender identity (Egan & Perry, 2001) and gender dysphoria. Measures are presently in construction that appreciate the complex nature of these two constructs and demonstrate the psychometric properties of reliability and validity (Zucker, 2005).

The information presented in this review is relevant to parents and professionals who must make a decision as to initial gender assignment in infants diagnosed with CAIS, PAIS, or micropenis. The diagnosis of CAIS is usually not made in infancy, but in adolescence when the girl fails to menstruate. Gender assignment at birth is female and is made automatically based on the perfect female appearance of the external genitalia. However, on occasion the diagnosis of CAIS is made when a newborn presents with female external appearing genitalia and the parents and their physician are expecting a male because amniocentesis had indicated XY chromosomes. In this case, the decision as to initial gender assignment is made more deliberate. The evidence provided herein supports the prevailing policy that such an infant diagnosed with CAIS be assigned and reared female.

In regard to infants presenting with a micropenis, the data on gender outcomes in this review do not favor one or the other gender of assignment. Nevertheless, I recommend raising most infants with micropenis as males. This recommendation is made because (a) no major medical interventions (e.g., feminizing surgery and later creation of a vagina) are necessary; (b) lifelong hormone (testosterone) therapy starting in adolescence to induce a male puberty may not be necessary although this depends on the diagnosis associated with the micropenis (e.g., hypogonadotropic hypogonadism); and (c) preservation of possible fertility. However, the recommendation for male rearing is provisional for this reason. The literature to date documents that a female gender identity apparently without gender dysphoria develops in XY individuals born with a micropenis and assigned female. If future

investigations can replicate this finding and show for female-reared persons that their quality of life, including sexual functioning and eroticism, is better than the quality of life in those reared male, then the recommendation to assign as male needs to be revisited.

Deciding gender assignment for infants with the diagnosis of PAIS remains challenging. Evidence reviewed herein does not provide clear guidelines. Diamond and Sigmundson (1997) proposed to base the gender assignment of infants with PAIS on the degree of virilization of the external genitalia, which is presumed to be a marker of androgen imprinting in the brain. However, the status of masculinization of the external genitalia is, at best, a crude estimate of such prenatal androgenization (Sobel & Imperato-McGinley, 2004). Review of 46,XX individuals born with congenital adrenal hyperplasia (CAH) and varying degrees of virilization of the external genitalia suggests that prenatal androgens do not usually interfere with the development of a female gender identity (Dessens, Slijper, & Drop, 2005). Furthermore, gender change, although infrequent, has not been shown to be correlated with a specific AR-gene defect. The reasons for self-initiated gender change in some individuals diagnosed with PAIS have yet to be elucidated.

In summary, most individuals with one of the intersex syndromes reviewed herein develop a gender identity commensurate with the gender they have been assigned in infancy. Gender dysphoria and gender change do occur, but at a low rate. Assignment of gender, while taking biologic criteria into account, is a social event. Long-term investigation integrating prenatal biological with postnatal biological and psychosocial variables, examples of which have been suggested by some investigators (Houk, Dayner, & Lee, 2004; Mazur, Sandberg, Perrin, Gallagher, & MacGillivray, 2004; Meyer-Bahlburg & Blizzard, 2004), may yield clues as to why some individuals with the same diagnosis changed gender and why the majority did not.

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