Long-Term Perspectives for 46,XY Patients Affected by Complete Androgen Insensitivity Syndrome or Congenital Micropenis

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ABSTRACT

Controversy concerning optimal treatment for individuals affected by syndromes of abnormal sex differentiation can best be resolved with knowledge about long-term medical, surgical, and psychosexual outcomes of patients. Follow-up information has recently been gathered on older cohorts of the following patient groups: (1) those affected by complete androgen insensitivity syndrome (CAIS) raised female and (2) those affected by congenital micropenis raised male or female. As a group, women with CAIS were satisfied with their female gender and sexual function. However, a need for better patient education was identified for this specific population. Most patients with congenital micropenis, whether raised male or female, were satisfied with their gender. Regardless of sex of rearing, dissatisfaction with the appearance and function of the genitalia as judged by both physicians and subjects was evident. For patients with congenital micropenis, male sex of rearing was concluded to be optimal because genital reconstructive surgery is not required with this choice.

KEYWORDS: Androgen insensitivity, micropenis, gender, sex, intersex

Public statements by intersex activist groups (www.isna.org) and medical case reports of the inability to accept assigned gender[1–3] have resulted in the reappraisal of medical, surgical, and psychological services offered to individuals affected by syndromes of abnormal sex differentiation.[4] Other articles in this issue review the genetic and physiological processes of sex differentiation as well as syndromes that occur when these processes do not proceed in typical ways (leading to what are commonly referred to as intersex conditions). The purpose of the present article is to review the long-term medical, surgical, and psychosexual outcome of 46,XY individuals affected by two specific intersex conditions, complete androgen insensitivity syndrome (CAIS) and congenital micropenis, with the aim of identifying optimal treatment guidelines.

Measures

Long-term outcome measures included subject-reported satisfaction with their physical appearance, gender development, sexual orientation, sexual function, and opinions pertaining to medical and surgical treatment. Physician-rated cosmetic appearance of the external genitalia and degree of patient knowledge were also documented.

Subjects

Adults treated in infancy and/or childhood at the Pediatric Endocrinology Clinic of the Johns Hopkins Hospital were invited to participate in long-term outcome studies of psychosexual development. Study invitations were extended to patients, 21 years or older, with a

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Table 1 Complete Androgen Insensitivity Syndrome (CAIS) and Micropenis Patients from the Johns Hopkins Pediatric Endocrine Clinic of the Johns Hopkins Hospital, 21 Years or Older*

	CAIS Females	Micropenis Males	Micropenis Females	Total
Participants	14	13	5	32
Chart not found	0	2	0	2
Unable to locate	4	8	2	14
Died	0	1	0	1
Cognitive impairment	0	7	4	11
Refused to participate	2	2	1	5
Total	20	33	12	65

*All patients affected by CAIS were raised female. Patients with congenital micropenis were raised either male or female.
Adapted from Wisniewski et al.[5,6]

46,XY chromosome complement affected by abnormal sex differentiation. Individuals who presented with female external genitalia as a result of CAIS or a micropenis without hypospadias were included in this report[5,6] (Table 1).

LONG-TERM OUTCOME OF COMPLETE ANDROGEN INSENSITIVITY SYNDROME

Several reports exist on the physical and psychosexual development of girls and young women with CAIS.[7–12] In our follow-up study of 14 women with CAIS, participants ranged in age from their mid-20s to their mid-60s[5] (Table 2). These participants represent an older cohort of women than what is typically studied, thus allowing for a more complete assessment of the long-term physical and psychosexual development in women with this particular intersex condition.

Table 2 Race, Age, and Androgen Receptor (AR) Gene Mutation for the 14 Women with Complete Androgen Insensitivity Syndrome (CAIS) Who Participated in Our Long-Term Outcome Study

ID	Race	Age (y)	AR Mutation
1	Caucasian	25–30	Exon 5
2	Caucasian	30–35	Exon 1
3	Caucasian	36–40	Exon 3
4	African American	36–40	Exon 3
5	Caucasian	36–40	Deletion
6	African American	36–40	Exon 5
7	African American	36–40	Exon 5
8	Caucasian	41–45	Deletion
9	Caucasian	41–45	Deletion
10	African American	46–50	Exon 5
11	Caucasian	46–50	Exon 7
12	Caucasian	51–55	Exon 4
13	Caucasian	56–60	Exon 7
14	Caucasian	61–65	Exon 7

Adapted from Wisniewski et al.[5]

Long-Term Physical Outcome

Subjects reported with a written questionnaire and during discussion at a physical examination on their degree of satisfaction with their physical appearance. The majority of adult women with CAIS (57%) reported satisfaction with their physical appearance. When dissatisfied, subjects were instructed to indicate which of their physical attributes contributed to dissatisfaction. Among those reporting mild to strong dissatisfaction, lack of sexual hair and youthful appearance were the major complaints.[5]

Two examining physicians rated the cosmetic appearance of the external genitalia and agreed that it was "good" for all subjects using the scale good 1 to 5 poor. None of the women required surgical feminization of their clitoris or labia.[5] This is not surprising as women with CAIS have normal female external genitalia at birth.

Some women with CAIS require vaginal lengthening for successful penovaginal intercourse because the posterior portion of their vagina fails to develop during fetal life due to the action of Müllerian-inhibiting substance (MIS).[13] Despite suppression of their Müllerian ducts, more than half of women with CAIS studied did not desire vaginal lengthening. In fact, many women had normal vaginal depth despite never receiving surgical lengthening.[5] These results support the management philosophy that vaginal reconstruction should be postponed until patients are ready to be sexually active.

Finally, women with CAIS as a group are tall.[9,14] This is probably due to the somewhat later onset of pu-

Table 3 Final Adult Height (Centile) Extrapolated from a Growth Chart for Women*

ID	Centile of Height for Women	Comparison with Weight Range of Healthy Women
1	95	0 kg
2	90	−7 kg
3	95	+ 80 kg
4	50	+ 38 kg
5	95	+ 95 kg
6	95	+ 82 kg
7	75	0 kg
8	75	+ 4 kg
9	90	− 3 kg
10	75	+ 9 kg
11	50	+ 33 kg
12	95	− 3 kg
13	50	+ 27 kg
14	90	+ 15 kg

*Adult weight (kg) in relation to statistical norms for women based on medium-build frames in terms of final height.
Adapted from Wisniewski et al.[5]

berty that occurs when testosterone produced by their testes is aromatized to estrogen. Although half of the women studied were obese in adulthood, this was not the case earlier in their lives. The rate of obesity mirrored that of American women in general for this older cohort of subjects[5] (Table 3).

Long-Term Gender Development

Women with CAIS retrospectively rated their degree of masculinity and femininity at childhood, adolescence, and adulthood with a written questionnaire (Fig. 1). As a group, these women showed greater femininity than masculinity throughout development.

In addition, subjects reported on their degree of satisfaction with their female sex of rearing. All women studied reported acceptance of their female gender. None of the women identified with having a male gender, nor did any ever consider a gender reassignment to that of a man.[5]

Sexual Orientation across Development

Subjects rated their degree of sexual attraction toward, fantasy about, and experience with men and women during adolescence and adulthood using a modified Kinsey scale.[15] All women retrospectively reported a female heterosexual orientation during their adolescence. Most women (93%) reported a female heterosexual orientation at adulthood.[5]

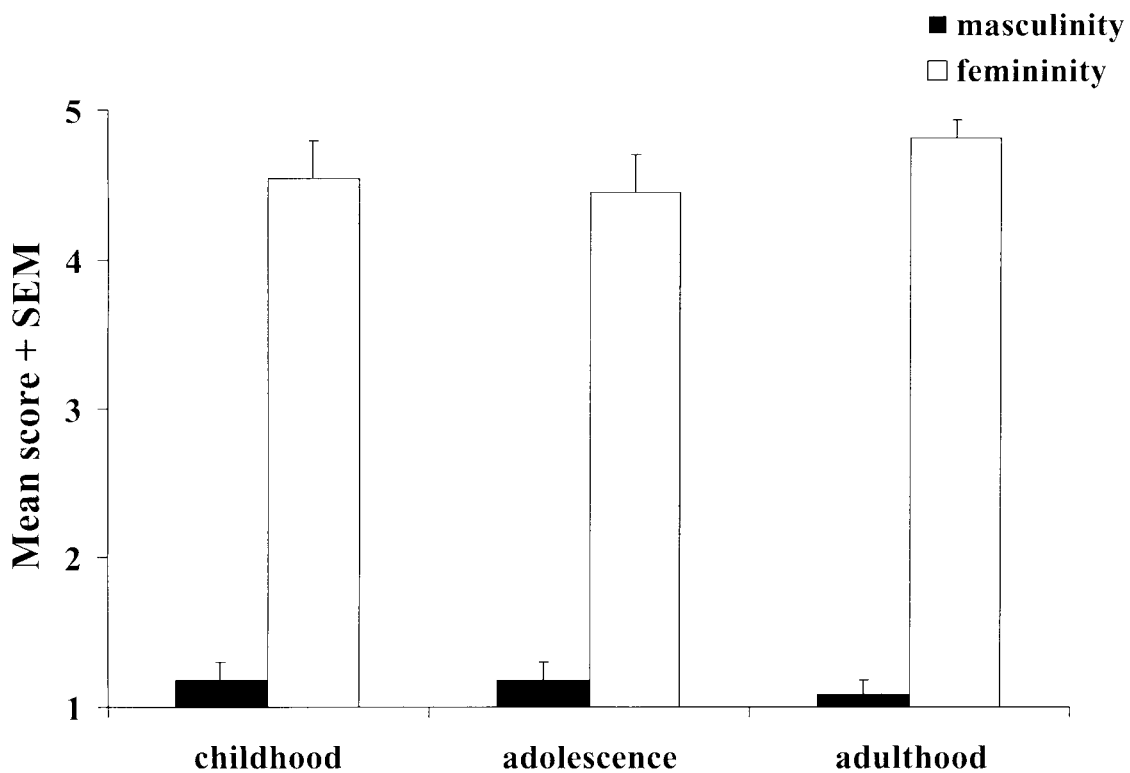

Figure 1 Mean + SEM masculinity and femininity scores for 14 women with CAIS. Ratings were retrospectively recalled from childhood, adolescence, and adulthood. A higher score signifies a greater degree of self-rated masculinity and femininity. (Adapted from Wisniewski et al.[5])

Long-Term Sexual Function

Subjects rated the adequacy of their genitalia specifically, and their satisfaction with sexual function in general,with a written questionnaire and during discussion at the physical examination. The majority of women (78%) reported satisfaction with their genitalia and many (71%) reported satisfaction with their sexual function in general. Subjects were also asked to rate the strength of their libido and to indicate whether they experienced orgasms. Despite their insensitivity to androgens, 71% of subjects reported their libido to be at least average in strength and 77% experienced orgasm[5] (Table 4).

Subject Satisfaction with Knowledge about CAIS

Subjects were assessed for their level of knowledge about CAIS, including their understanding of their karyotype, gonadal development, and importance of estrogen replacement therapy following gonadectomy. More than half of the women studied (57%) expressed a limited understanding of CAIS (Table 5). Women were also asked to rate their degree of satisfaction with their knowledge about CAIS at the time of study participation. Approximately one third of the women (36%) were dissatisfied with their level of understanding.[5] As indicated in Table 5, level of knowledge of CAIS did not always predict subject satisfaction with this knowledge. Of the eight women who exhibited a limited understanding of CAIS, half were satisfied with their knowledge.

Table 4 Adequacy of Genitalia for Sexual Function, Satisfaction with Sexual Function in General, Strength of Libido, and Experience of Orgasm in a Group of Women with CAIS

ID	Adequacy of Genitalia	General Sexual Satisfaction	Strength of Libido	Orgasm
1	1	1	*3	Yes
2	2	2	5	Yes
3	1	1	*4	Unsure
4	1	3	*4	No
5	2	3	5	Unsure
6	1	1	*4	Yes
7	1	1	5	Yes
8	1	1	4	Yes
9	1	1	3	Yes
10	3	3	*0	—
11	1	1	2	Yes
12	1	1	4	Yes
13	1	1	4	Yes
14	1	1	4	Yes

*Indicates women who were not compliant with estrogen replacement therapy following gonadectomy and — indicates no response was provided. The following scales were used: Adequacy of genitalia for sexual function: adequate 1 . . . 2 . . . 3 totally inadequate. Satisfaction with general sexual function: mainly satisfied 1 . . . 2 . . . 3 mainly dissatisfied. Strength of libido in comparison with other age-matched women: 0 = none; 1 = very low; 2 = low; 3 = lower than average; 4 = average; 5 = higher than average; 6 = high; 7 = very high.
Adapted from Wisniewski et al.[5]

LONG-TERM OUTCOME OF CONGENITAL MICROPENIS

A micropenis refers to a normal but small (<2.5 standard deviations [SD] below the mean for age) penis without hypospadias.[16,17] This condition can occur in genetic males affected by hypergonadotropic hypogonadism, hypogonadotropic hypogonadism, or partial androgen insensitivity syndrome (PAIS) or can be idiopathic in nature[17]. Compared with CAIS, fewer outcome studies have been conducted on individuals born with a micropenis, raised either male or female.

Follow-up of patients with congenital micropenis attributed to various causes has revealed that for the patients raised male, final penile size tends to be small and subjects report stigmatization regarding their genitalia.[18–20] Little is known about the long-term physical or psychological development of patients with congenital micropenis reared female. In a manner similar to that used with CAIS, our group documented outcome information for an older cohort of patients with congenital micropenis reared male (Table 6) or female (Table 7).[6]

Table 5 Knowledge of CAIS and Satisfaction with this Knowledge in a Group of 14 Women Affected by This Condition

ID	Knowledge About CAIS	Satisfaction with Knowledge
1	2	Yes
2	3	Yes
3	1	No
4	1	No
5	3	No
6	1	No
7	1	Yes
8	3	Yes
9	3	Yes
10	1	No
11	1	Yes
12	3	Yes
13	1	Yes
14	1	Yes

The following scale was used: Level of patient knowledge pertaining to CAIS: 1 = no knowledge; 2 = some knowledge; 3 = excellent knowledge. Adapted from Wisniewski et al.[5]

Table 6 Race, Age, and Etiology of Congenital Micropenis for 13 Subjects Reared Male who Participated in Our Long-Term Outcome Study

ID	Race	Age (y)	Etiology
1	Caucasian	21–25	Idiopathic
2	Caucasian	21–25	Hypergonadotropic hypogonadism
3	African American	26–30	Kallmann's syndrome
4	Caucasian	31–35	Kallmann's syndrome
5	Caucasian	31–35	Idiopathic
6	Caucasian	36–40	Kallmann's syndrome
7	Caucasian	36–40	Panhypopituitarism
8	Caucasian	41–45	Kallmann's syndrome
9	Caucasian	41–45	Kallmann's syndrome
10	African American	41–45	Kallmann's syndrome
11	Caucasian	41–45	Panhypopituitarism
12	Caucasian	41–45	Panhypopituitarism
13	Caucasian	41–45	Hypergonadotropic hypogonadism

Adapted from Wisniewski et al.[6]

Long-Term Physical Outcome

Similar to participants in the CAIS follow-up study, subjects with congenital micropenis reported with a questionnaire and at physical examination on their satisfaction with their physical appearance. Stretched penile length for subjects living as men at the time of participation varied by etiology and compliance with testosterone therapy. The majority (66%) were dissatisfied with the size of their penis. Among nine men receiving testosterone therapy, stretched penile length was between the mean and −2 SD for four men, at −2 SD for three, and below 2 SD for two. Among four men not receiving testosterone, stretched penile length was in the normal range for one man who produced his own testosterone endogenously and was 4 to 7 SD below the mean for the men who did not.

The size of the testes was small for most men who had either hyper- or hyposecretion of gonadotropins. In addition, for the men who were treated with testosterone, hormone therapy contributed to their having small testes. Aside from a small penis and testes, dissatisfaction with physical development was also attributed to inadequate sexual hair (50%) and gynecomastia (33%) by some of the men studied.[6]

Three subjects (60%) living as women at the time of participation had a normal vagina in terms of vaginal length following vaginoplasty. The remaining two women chose not to have a vagina created surgically. All women received surgical feminization of their external genitalia during early childhood. One woman received a rating of "good" by physicians for the cosmetic appearance of her external genitalia. Contributing to the "fair" rating received by the remaining four women (80%) were an absent clitoris and/or labia minora, an unusual placement of the vaginal introitus on the perineum, and an unusual appearance of the introitus.[6]

Table 7 Race, Age, and Etiology of Congenital Micropenis for Five Subjects Reared Female who Participated in Our Long-Term Outcome Study

ID	Race	Age (y)	Etiology
1	Caucasian	21–25	Undetermined
2	Caucasian	21–25	Panhypopituitarism
3	Caucasian	26–30	Hypogonadotropic hypogonadism
4	Caucasian	26–30	Hypergonadotropic hypogonadism
5	Caucasian	26–30	Panhypopituitarism

Adapted from Wisniewski et al.[6]

Long-Term Gender Development

Subjects with congenital micropenis currently living as men and women retrospectively rated their masculinity and femininity at adulthood with a written questionnaire. Men were more masculine than feminine and women more feminine than masculine throughout their development (Figs. 2 and 3).

Concerning satisfaction with sex of rearing, 12 subjects with congenital micropenis reared male (92%) were satisfied with their sex of rearing. All five subjects with congenital micropenis reared female were satisfied with their sex of rearing; however, four (80%) had questioned their sex of rearing at times in their lives (Table 8).[6]

Sexual Orientation across Development

Using a modified Kinsey scale, subjects classified their sexual orientation. Ten subjects living as men (77%) reported a male heterosexual orientation. Three subjects

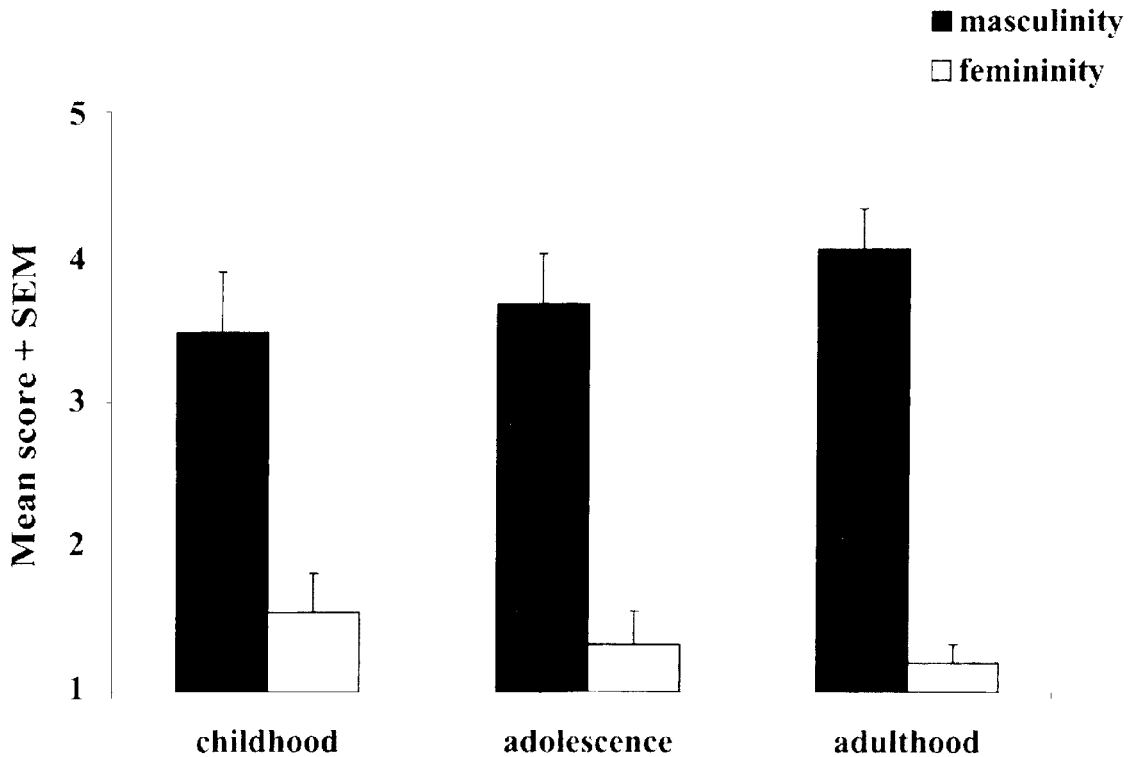

Figure 2 Mean + SEM masculinity and femininity scores for 13 men with congenital micropenis. Ratings were retrospectively recalled from childhood, adolescence, and adulthood. A higher score signifies a greater degree of self-rated masculinity and femininity. (Adapted from Wisniewski et al.[5])

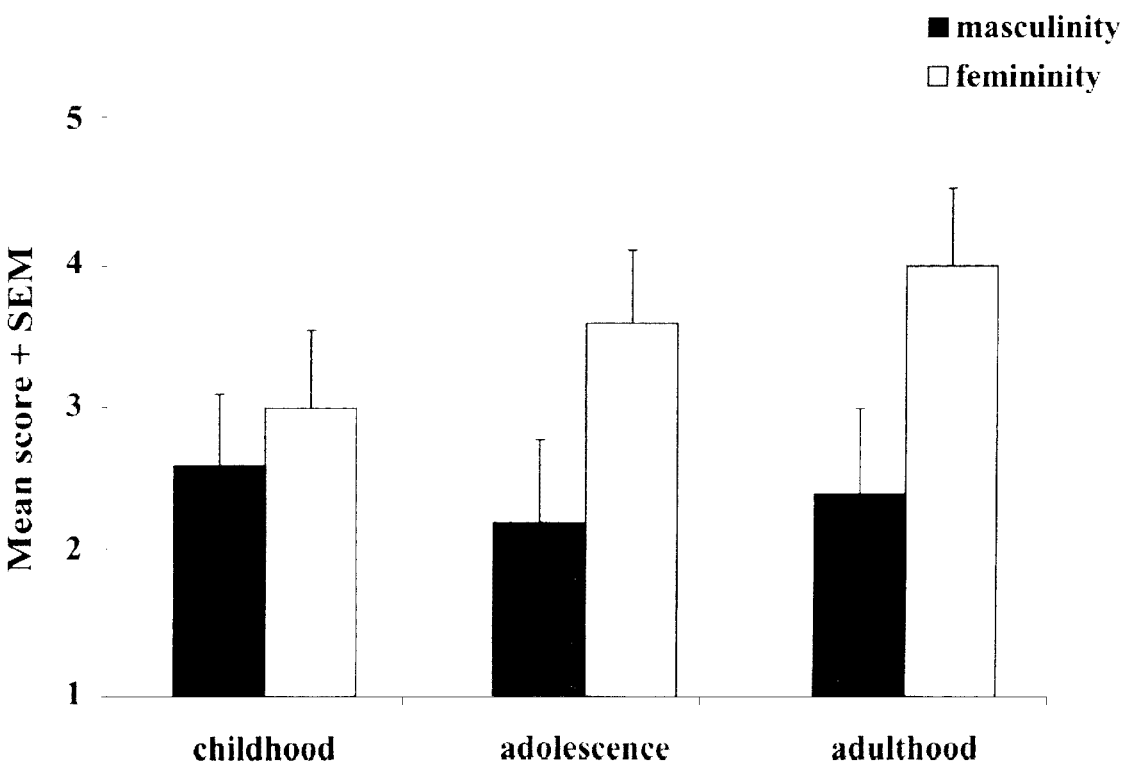

Figure 3 Mean + SEM masculinity and femininity scores for five women with congenital micropenis. Ratings were retrospectively recalled from childhood, adolescence, and adulthood. A higher score signifies a greater degree of self-rated masculinity and femininity. (Adapted from Wisniewski et al.[6])

Table 8 Age at Female Gender Assignment, Long-Term Satisfaction with Female Gender, and Doubts Regarding Female Gender in Five Subjects with Congenital Micropenis Reared Female

ID	Age at Female Sex Assignment (mo)	Adult Satisfaction with Female Gender	Ever Doubted Female Gender?
1	13/12	Satisfied	Yes (adolescence)
2	22/12	Satisfied	No
3	16/12	Satisfied	Yes (adolescence)
4	18/12	Satisfied	Yes (adolescence and adulthood)
5	33/12	Satisfied	Yes

Adapted from Wisniewski et al.[6]

living as women (60%) reported a female heterosexual orientation. The remaining subjects classified themselves as homosexual, bisexual, and asexual.[6]

Long-Term Sexual Function

Half of the men who responded (6 out of 12) were satisfied with their genitalia in terms of sexual functioning. Seven men (58%) reported having erections of "good" quality and all of the men were able to ejaculate. Eight men (67%) reported a libido that was average in strength or stronger. In contrast to the majority of men who were satisfied with their sexual function, only one woman (20%) with congenital micropenis was satisfied with her genitalia for sexual functioning. Three women (60%) reported their libido to be of average strength or stronger and also experienced orgasms. The remaining two women who reported both an absence of both libido and orgasm had received an amputation of their phallus when assigned to the female gender.[6]

Subject Satisfaction with Knowledge about Congenital Micropenis

Subjects were evaluated on their degree of knowledge about congenital micropenis including appearance of their genitalia at birth and etiology underlying their condition. For subjects raised female, knowledge of female gender reassignment was also evaluated. The majority of men (67%) and women (80%) exhibited a good degree of knowledge pertaining to their medical history.[6]

SUMMARY AND IMPLICATIONS FOR MANAGEMENT OF CAIS AND CONGENITAL MICROPENIS

As a result of following patients with CAIS or congenital micropenis into adulthood, we were able to learn about the difficulties these conditions (and their treatment) place on a sexually mature person. Women with CAIS were largely satisfied with their female gender and sexual function. The greatest need for improvement identified for this population was to increase the level of understanding of CAIS in affected women.

Similar to the CAIS group, patients with congenital micropenis reared male or female were also largely satisfied with their respective genders. In contrast to patients with CAIS, those with congenital micropenis reported a greater degree of dissatisfaction concerning their sexual function and treatment options. Whereas those raised male had a small penis that caused them disappointment, women were unhappy with the functional outcome of their female genital construction. In addition, many of the subjects affected by congenital micropenis had to treat multiple endocrine abnormalities related to abnormal anterior and posterior function of their pituitary gland. Because female sex of rearing did not spare patients with congenital micropenis from many of the problems experienced by those raised male who did not require genital surgery, we conclude that male sex of rearing is optimal for this particular intersex condition.

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