Complete Androgen Insensitivity Syndrome: Long-Term Medical, Surgical, and Psychosexual Outcome*

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ABSTRACT

Controversy concerning the most appropriate treatment guidelines for intersex children currently exists. This is due to a lack of long-term information regarding medical, surgical, and psychosexual outcome in affected adults. We have assessed by questionnaire and medical examination the physical and psychosexual status of 14 women with documented complete androgen insensitivity syndrome (CAIS). We have also determined participant knowledge of CAIS as well as opinion of medical and surgical treatment. As a whole, secondary sexual development of these women was satisfactory, as judged by both participants and physicians. In general, most women were satisfied with their psychosexual development and sexual function. Factors reported to contribute to dissatisfaction were sexual abuse in one case and marked obesity in another. All of the women who participated were satisfied with having been raised as females, and none desired a gender reassignment. Although not perfect, the medical, surgical, and psychosexual outcomes for women with CAIS were satisfactory; however, specific ways for improving long-term treatment of this population were identified. (J Clin Endocrinol Metab 85: 2664–2669, 2000)

THE RELATIVE contributions of variables such as prenatal hormones and social rearing to psychosexual development have been studied in a variety of intersex populations (1–6). These investigations have led to the wide acceptance of a multivariate conceptualization of gender development that emphasizes the importance of both nature and nurture (7–9).

Recent reports of psychosexual outcome in two penis ablation patients (10, 11) have led to reconsideration of sex assignment practices for intersexuals. One of the issues raised by these reports is the possibility that fetal androgen exposure influences the brains of such patients, resulting in male-typical psychosexual development. However, reports of psychosexual development in penis ablation patients are conflicting, and to date it remains unclear how treatment of intersex patients should be revised (12).

If androgens alone are important for male psychosexual development, then a group of intersex patients with complete androgen insensitivity syndrome (CAIS) would not be expected to exhibit a male bias, as they have a complete end-organ resistance to androgenic effects. However, other variables related to CAIS, such as the presence of a Y-chromosome, testes and shallow vagina, have been suggested to pose obstacles to healthy psychosexual development in this group (13). Additionally, CAIS women provide an ideal opportunity to investigate potential influences of estrogens on gender development in 46,XY individuals who are unresponsive to androgens (14).

Subjects and Methods

The research reported here was approved by the Joint Committee of Clinical Investigations of The Johns Hopkins University School of Medicine, The Johns Hopkins Hospital (Baltimore, MD). Written, informed consent was obtained from all subjects before participation. Participants were asked to complete a written questionnaire before their physical examinations. During the physical examination, participants were asked to confirm their original questionnaire responses and also to elaborate on responses that were unclear or for which the participant desired further discussion.

Diagnostic criteria for CAIS subjects

CAIS diagnosis was based on the following: 1) presence of testes along with normal female external genitalia in a 46,XY individual, 2) identification of an androgen receptor (AR) gene mutation, 3) spontaneous feminization (but with no menses) at puberty before gonadectomy with no virilization despite normal or high male levels of testosterone,


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TABLE 1. Information regarding race, age, androgen receptor gene mutation, ages at surgeries, and appearance of genitalia for CAIS subjects at time of participation

<table>
<thead>
<tr>
<th>ID no.</th>
<th>Race</th>
<th>Age (yr)</th>
<th>Androgen receptor gene mutation</th>
<th>Adult sexual hair</th>
<th>Age (yr) at gonadectomy</th>
<th>Age (yr) at vaginoplasty</th>
<th>Length of clitoris (cm)</th>
<th>Depth of vagina (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Caucasian</td>
<td>25–30</td>
<td>Exon 5</td>
<td>Minimal</td>
<td>14</td>
<td>None</td>
<td>1</td>
<td>12</td>
</tr>
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<td>2</td>
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<td>30–35</td>
<td>Exon 1</td>
<td>Minimal</td>
<td>2</td>
<td>None</td>
<td>1.5</td>
<td>8.5</td>
</tr>
<tr>
<td>3</td>
<td>Caucasian</td>
<td>36–40</td>
<td>Exon 3</td>
<td>None</td>
<td>16</td>
<td>None</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>African-American</td>
<td>36–40</td>
<td>Exon 3</td>
<td>None</td>
<td>19</td>
<td>None</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>Caucasian</td>
<td>36–40</td>
<td>Deletion</td>
<td>Minimal</td>
<td>17</td>
<td>17, 35</td>
<td>0.75</td>
<td>14</td>
</tr>
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<td>18</td>
<td>None</td>
<td>1</td>
<td>13</td>
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<tr>
<td>7</td>
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<td>36–40</td>
<td>Exon 5</td>
<td>Minimal</td>
<td>15</td>
<td>None</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
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<td>41–45</td>
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<td>18</td>
<td>None</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>Caucasian</td>
<td>41–45</td>
<td>Deletion</td>
<td>Minimal</td>
<td>17</td>
<td>None</td>
<td>0.2</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>African-American</td>
<td>46–50</td>
<td>Exon 5</td>
<td>Minimal</td>
<td>16</td>
<td>16</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>Caucasian</td>
<td>46–50</td>
<td>Exon 7</td>
<td>Minimal</td>
<td>16</td>
<td>16</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
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<td>51–55</td>
<td>Not available</td>
<td>Minimal</td>
<td>13</td>
<td>21</td>
<td>0.1</td>
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</tr>
<tr>
<td>13</td>
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<td>56–60</td>
<td>Exon 7</td>
<td>Minimal</td>
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<td>20</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>Caucasian</td>
<td>61–65</td>
<td>Exon 7</td>
<td>Minimal</td>
<td>21</td>
<td>21</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>
Participants’ opinions concerning timing of surgical treatment/third sex. Participants were asked their opinion regarding appropriate timing of gonadectomy and vaginoplasty in a written questionnaire and during the physical examination. Although the question of optimal timing for surgical treatment of intersex patients has focused on the reconstruction of ambiguous external genitalia, surgical modification of gonadal and posterior vaginal status in CAIS women also leads to permanent consequences and therefore should be considered in this patient group.

Participants were asked their opinion regarding the categorization of intersex children as a “third gender” in opposition to the more traditional categories of male or female. Although this third gender classification usually applies to individuals with ambiguous external genitalia, it can be extended to CAIS women who possess a Y-chromosome and testes. Participants were also asked if they agreed with the concept of recognizing a third intersex category within our society as an alternative to treating intersex patients as either males or females. This question was included due to suggestions that intersex patients should not be raised according to strictly male or female categories (21, 22).

Results

Physical measurements at birth
Mean birth weight for participants was 3.5 kg (range, 2.26–4.1 kg), which did not differ from that of the general population (3.4 kg; range, 2.5–4.6 kg) (24). External genitalia was completely female with no abnormalities at birth for all participants.

Physical measurements in adulthood
Adult height of eight subjects (57%) fell at or exceeded the 90th percentile of the range of control adult females. Adult height of the remaining women (43%) fell between the 50th and 75th percentiles. Seven participants (50%) were within ±10 kg of their ideal weight range. The remaining seven participants exceeded their ideal weight by 15 kg or more, three of whom exceeded their ideal by 80 kg or more.

Most gonadectomies and vaginoplasties were performed on participants during their adolescence or adulthood (Table 1). Eight participants did not require vaginoplasty for peno-vaginal intercourse (one was homosexual), and one woman required vaginoplasty twice. Vaginoplasty consisted of a McIndoe partial thickness skin graft in all cases. Both examining physicians rated the appearance of the external genitalia as good for all women. Average clitoral length was 0.83 cm (range, 0.1–1.5 cm); no participant exhibited clitoral enlargement, and none required clitoroplasty. The eight women who did not experience vaginoplasty had an average vaginal length of 9 cm (range, 4.5–13 cm). The six women with a history of vaginoplasty had an average vaginal length of 8.6 cm (range, 4.5–14 cm). These measures are consistent with previous measures of mean vaginal length ranging from 7–11 cm (25–27). All women had breast development, with wide variability in breast size (range, 16 × 14 to 41 × 31 cm).

Regarding the occurrence of other medical conditions among CAIS women, obesity (43%) and bone loss (43%) were both reported most frequently (Table 2).

The degree of compliance with estrogen replacement therapy was determined for all participants based on information obtained from written questionnaire responses, medical charts, and discussion during the physical examination. Nine participants reported that they were compliant, whereas the remaining five women reported they had not taken estrogen replacement for most of their adult lives after gonadectomy.

Knowledge of medical history
Participants reported their level of satisfaction regarding their knowledge of AIS in a written questionnaire. Participants were also evaluated by a pediatric endocrinologist (C.J.M.) and psychologist (A.B.W.) to determine their level of understanding of AIS at the time of study participation. Specifically documented was participants’ knowledge of their gonadal development, karyotype, and importance of estrogen therapy as presented in our Patients’ Guide to Syndromes of Abnormal Sex Differentiation (23).

Statistical analysis
Due to the unique nature of CAIS, it is impossible to identify an appropriate control group. Additionally, the low frequency of this syndrome in the general population led to data presentation in the form of descriptive statistics and raw data.

Physical measurements at birth

<table>
<thead>
<tr>
<th>ID no.</th>
<th>Medical and psychiatric conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>2</td>
<td>Osteoporosis, breast fibroid cysts, scoliosis</td>
</tr>
<tr>
<td>3</td>
<td>Obesity, hypothyroid, high cholesterol</td>
</tr>
<tr>
<td>4</td>
<td>Obesity</td>
</tr>
<tr>
<td>5</td>
<td>Obesity, osteoporosis</td>
</tr>
<tr>
<td>6</td>
<td>Obesity, diabetes II, asthma</td>
</tr>
<tr>
<td>7</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>8</td>
<td>Bulemia, osteoporosis</td>
</tr>
<tr>
<td>9</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>10</td>
<td>Depression, drug addiction, poor general health</td>
</tr>
<tr>
<td>11</td>
<td>Obesity, high cholesterol, asthma, high blood pressure</td>
</tr>
<tr>
<td>12</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>13</td>
<td>Obesity, hernias</td>
</tr>
<tr>
<td>14</td>
<td>Osteoporosis, stroke, gall stones</td>
</tr>
</tbody>
</table>
Self-perceived femininity and masculinity. Women with CAIS overwhelmingly reported a high degree of femininity along with a low degree of masculinity throughout development. Mean femininity rating (not feminine = 1 to highly feminine = 5) for subjects during childhood was 4.4 (range, 2–5), during adolescence was 4.2 (range, 3–5) and during adulthood was 4.6 (range, 4–5). Mean masculinity rating (not masculine = 1 to highly masculine = 5) for subjects during childhood was 1.4 (range, 1–4), during adolescence was 1.4 (range, 1–3), and during adulthood was 1.1 (range, 1–2).

Sexual orientation. A large majority of CAIS women reported female heterosexual orientation in terms of sexual attraction, fantasies, and experience during both adolescence (100%) and adulthood (93%). The one participant who reported homosexual attraction, fantasies, and experiences indicated that a lesbian orientation applied only to her adulthood. Clearly, in this case the development of female homosexuality was not associated with androgen exposure.

Marriage and motherhood. Seven women (50%) were married at the time of participation, and the mean age at first marriage was 27 yr (range, 16–38 yr). Five of these and one unmarried woman (43%) were mothers through adoption. Of the seven participants who were not married, one was engaged, one was homosexual, one was not interested in marriage, and the remaining four women expressed a desire for marriage to a man but had not yet met a satisfactory partner.

Satisfaction with sex of rearing. CAIS women unanimously reported satisfaction with being a woman (100%). Two participants (18%) questioned their physical status as women, but none reported a desire to change sex to that of a man.

Participants’ opinions of timing of surgical treatment/third sex. The majority of women who responded indicated the most appropriate timing for their surgical procedures was during adolescence or adulthood (8 of 10 respondents, or 80%). Two women reported the most appropriate timing for surgery was during infancy.

The vast majority of participants (81% of the 11 who responded) did not approve of rearing intersex children according to a third gender.

Long-term psychological treatment

The majority of CAIS women studied received some form of counseling (83%) at various ages and for various lengths of time (1–15 yr) concerning aspects of their syndrome.

Knowledge of medical history

Eight CAIS women (57%) exhibited no understanding of CAIS (i.e. were unaware of their karyotype, gonadal characteristics, or the importance of estrogen replacement) at the time of participation, and only 64% indicated that they were satisfied with their level of knowledge regarding their condition. It could not be determined if participants ever received information about their syndrome or if they were previously informed but did not recall the information. Nevertheless, this finding emphasizes the importance of following CAIS patients into adulthood and subsequently offering them adult education about their syndrome.

Discussion

To determine the natural history of CAIS and long-term outcome of treatment intervention, it is necessary to follow affected individuals over time. Previous knowledge of CAIS has been based on studies of relatively young patients. Such young CAIS women overwhelmingly report contentment with being female, a desire for marriage and motherhood, sexual attraction and practice exclusively oriented toward men, as well as the ability to experience orgasms (16–18, 28). However, it is likely that older women have the benefit of greater experience with their gender and sexuality compared to younger women and girls. The present study extends our knowledge of CAIS to an older cohort of women.

Furthermore, quality of sexual function and appearance of genitalia and secondary sexual characteristics were considered in conjunction with our psychosexual evaluation. Previous psychosexual studies of intersex patients have not consistently assessed outcome of medical and surgical treatment in terms of sexual function and appearance. It is likely that factors such as an individual’s cosmetic appearance and quality of sexual function influence gender and sexuality, and therefore should be considered in psychosexual outcome research concerning intersex populations.

Physical

CAIS babies appeared no different from unaffected infants in terms of birth weight or genital appearance. Consistent with previous reports, CAIS women tend to be tall (29, 30) and experience normal feminization of secondary sexual characteristics, with the exception of lacking female-typical amounts of axillary and pubic hair in adulthood (31). Interestingly, 12 participants had a minimal amount of fine, soft pubic hair but no axillary hair. This is consistent with previous observations in this group of vellus down on the body that is not androgen dependent (32). Aside from lacking sexual hair, the external genitalia of all participants appeared normal. Six women (43%) had undergone vaginoplasty, but none required or had clitoroplasty.

Psychosexual

Most CAIS women were satisfied with their sexual functioning. However, three (21%) were dissatisfied. Of these, one did not receive any genital reconstructive surgery despite a shallow vaginal depth and thinks she would be unable to participate in peno-vaginal intercourse. Although this woman has never attempted peno-vaginal intercourse, she has discovered great satisfaction from homosexual sexual activity. The remaining two had undergone vaginoplasties that resulted in sufficient vaginal length for peno-vaginal intercourse. Their dissatisfaction may be related to other variables. One woman was a victim of sexual abuse early in life and is presently in poor health resulting from substance abuse; the other reported severe dissatisfaction with her body image.

Libido and ability to experience orgasms were not a problem for the CAIS women in this study. This illustrates that although androgens may contribute to libido and orgasmic potential in non-CAIS women (33–35), libido and orgasm can
be experienced by women who exhibit complete end-organ insensitivity to androgens. Furthermore, there were no differences in self-reported libido based on compliance with estrogen therapy. Vaginal lubrication is another characteristic of sexual functioning thought to be related to estrogen levels. No participant reported difficulty with vaginal lubrication on the written questionnaire or during the physical examination.

Despite some of the unhappiness with physical attributes, the majority of women with CAIS were mainly satisfied with their physical appearance.

CAIS women overwhelmingly perceive themselves as highly feminine and not masculine throughout development. Additionally, CAIS women largely report their sexual attraction, fantasies, and experiences were best described as female heterosexual. Concerning the one woman who reported heterosexual attraction and fantasies in adolescence followed by homosexual thoughts and actions in adulthood, perhaps a short vagina coupled with fear of vaginoplasty contributed to this change. Several women were married and/or mothers. All participants reported being mainly satisfied when asked their degree of satisfaction in being a woman. Of the two women who stated that they questioned their physical status as women, one responded that this was due to her inability to menstruate and become pregnant, and the other reported that this was in response to media articles she encountered regarding intersexuality.

**Treatment**

Several issues of long-term health status are of concern in our CAIS participants. First, long-term compliance with estrogen replacement is less than optimal in this group. Second, older CAIS women as a group are obese. However, obesity among women with CAIS mirrors rates observed in the population of American women at large and does not appear to be directly related to this condition (36, 37). Lastly, women with CAIS appear at to be at risk for bone-related disease. It is unclear at this time, however, if this is a result of androgen insensitivity per se, a consequence of inadequate estrogen replacement, or both (38).

Most women (80% who responded) sought psychological counseling at some point in development, as indicated by the written questionnaire. The majority of participants did not believe a third gender category was appropriate for intersex patients. These points stress the importance of providing well rounded care to these patients that includes counseling services as well as medical and surgical care.

The great majority of these CAIS women (78%) reported that the most appropriate timing of gonadectomy and vaginoplasty procedures was during adolescence or adulthood. More than half (64%) did not fully understand their diagnosis in adulthood, and the majority indicated a desire to better understand their condition. However, all women stressed the importance of confidentiality regarding their condition. These results support the concerns of CAIS patient advocacy groups regarding the disclosure of medical information to patients and the postponement of vaginoplasty to late adolescence or adulthood for CAIS patients (8, 39).

Complete insensitivity to androgen action is clearly an extreme in the spectrum of congenital malformations of sex organs. Additional studies of long-range outcome of subjects with partial AIS and other conditions associated with ambiguous genital development are in progress.

**References**