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Androgen insensitivity syndrome and Klinefelter's syndrome: sex and gender considerations

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The androgen insensitivity syndrome (AIS) and Klinefelter's syndrome (KS), which usually are the province of endocrinologists and geneticists, present features of importance to psychiatrists and other psychotherapists. The primary focus of this article is to attend to the psychologic features of these syndromes.

Although not common, these conditions are not rare. They are among the most commonly seen intersex conditions and have a prevalence of 2 or 3 cases/1000 population. These conditions present instances of undermasculinization and both syndromes can occur in the same individual [1].

The medical-clinical-molecular characteristics of these conditions are covered in detail elsewhere [2–6]. We start with a brief introduction to the medical nature of each of these syndromes before proceeding to psychologic and social considerations.

Androgen insensitivity syndrome

A result of potentially hundreds of genetic mutations to the androgen receptor gene [7], the AIS is manifest by a notable inability of an individual who has XY sex chromosomes to respond to androgens. This inability occurs despite the presence of testes and typical testosterone production, transport, and metabolism [8]. Of particular consequence is the relative or complete failure of the individual to respond to testosterone or dihydrotestosterone that is crucial for the organi-

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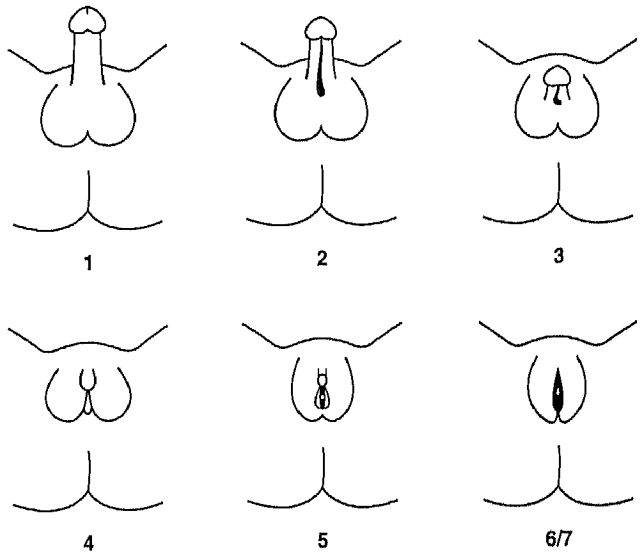

Fig. 1. Schematic representation of a grading scheme for clinical classification of AIS. Grades are numbered 1 through 7 in order of increasing severity (more defective masculinization). Grade 1: normal masculinization in utero; grade 2: male phenotype with mild defect in masculinization (eg, isolated hypospadias); grade 3: male phenotype with severe defect in masculinization—small penis, perineoscrotal hypospadias, bifid scrotum or cryptorchidism; grade 4: severe genital ambiguity—clitoral-like phallus, labioscrotal folds, single perineal orifice; grade 5: female phenotype with posterior labial fusion and clitoromegaly; grade 6/7: female phenotype (grade 6 if pubic hair present in adulthood, grade 7 if no pubic hair in adulthood). (*Adapted from* Quigley CA, DeBellis A, Marschke KB, El-Awady MK, Wilson EM, French FS. Androgen receptor defects: historical, clinical, and molecular perspectives. Endocrine Rev 1995;16(3):282; with permission.)

zation and activation of the anatomic and neural features that are needed for typical male development [5,9,10].

Persons who have AIS have genitalia that can look typically female in appearance (complete AIS; CAIS) or ambiguous with features that range from typical male-like to typical female-like (partial AIS; PAIS) (Fig. 1). Tissue response to estrogen is present and breast development and other signs of feminization occur. Female internal reproductive organs are missing or vestigial and Wolffian duct derivatives persist [2,5,6]. No relation between gene mutation and phenotype has been discovered. Infertility is common.

Persons who have CAIS appear female at birth and are reared as girls. Unless there is known or suspected AIS in the family or inguinal testes are detected, these girls typically go undiagnosed until puberty. The vagina may be short and blind-ending and may or may not need elongation [11]. Breast development occurs but pubic and axillary hair development is sparse or absent. When menses fails to occur a remedy is sought. Those who have PAIS usually are noticed at, or

soon after, birth. Depending upon the degree of masculinization of the genitals, the child may be raised as a boy or a girl.

AIS is an inherited condition that is propagated as a recessive X-linked single gene syndrome that can manifest differently in children of the same parents; one child in a family can be raised as a boy, whereas another can be raised as a girl [12].

A study of individuals in the United Kingdom, who had AIS and were 16 years of age or younger, found that 59% of those who were identified as having PAIS were assigned as males [13]. Most published cases of clinical-psychiatric involvement, however, seem to be related to subjects who were raised as females.

In contrast with, and usually of greater impact on the person than any medical morbidity, are the psychologic concomitants to the syndrome and management of related psychological problems. Concerns vary, depending upon whether the individual has the complete or partial form of the condition, if the individual was raised as boy or girl, at what age the syndrome was diagnosed, how much secrecy there was about the diagnosis, and the degree of open communication between the person, parents, and physicians. Management of the condition also is related to how much freedom the individual had in expressing feelings and behaviors. The following discussion derives from the work of other investigators and our population study of 39 persons who had CAIS and 18 persons who had PAIS.[1]

Psychiatric considerations

Secrecy, shame, stigma

Among our respondents and according to the findings of other investigators [14], the issues that cause the most difficulties for individuals who have AIS are connected to secrecy, shame, and stigma. Many complaints originate from not being informed about the diagnosis and its implications [15]. It was believed commonly that informing the individual as to the diagnosis would be traumatic and detrimental to rearing [16]. Among our own sample, not a few persons complained that, although they had undergone several routine physical examinations, they found out about their condition on their own and then sought medical attention and clarification. They, like others [15,17], found out about their AIS by way of a deliberate library search, by Internet browsing, or by some chance occurrence and were prompted to do so by features of their medical management, overheard gossip, or "gut feelings" that aroused suspicion.

[1] The individuals for our study originally were recruited from AIS support groups in the United Kingdom and the United States. Eventually, by way of referral from clinical colleagues and a listing of our research interests on an AIS website, others volunteered to participate. All study participants had confirming diagnosis of the CAIS or PAIS form of the condition. Respondents were interviewed in person and by way of an extensive written questionnaire. The second author of this article has AIS.

Often, when CAIS was diagnosed first at puberty, the patients were told a fabrication about faulty ovaries or another reason why they would need to undergo surgery. It is believed now that secrecy is detrimental and that persons who have AIS and other intersex conditions should be informed as to their condition [18–20]. Following diagnosis, only 51% of our respondents were told by their physician that they had AIS. When our respondents were asked if they ever believed that it was appropriate to not tell a person who had AIS about their condition only six answered, "yes," but only if the person were suicidal or specifically expressed a desire not to know.

After finding out about their condition, most persons felt depressed—some to the point of breakdown. Others experienced denial or shock. After learning the truth, one of the first questions that patients ask has to do with whether their parents had known about the condition. Secrecy is considered a breach of trust and is harmful [20,21]. Many patients come to realize that their parents were unaware of the condition or were told by doctors to preserve the secret.

Only 9 of our 57 respondents (16%) were offered counseling by their physicians. More than half of our study subjects subsequently sought out a psychiatrist or other therapist.

Not occasionally, patients' awareness and difficulty in dealing with their AIS was compounded by the health care system. We, and other investigators [22,23] found that many of our population were treated as medical oddities, were subjected to repeated examinations, and were displayed to medical colleagues or students or photographed without their permission. The outmoded term "testicular female" was used frequently and insensitively in describing their condition to them. A lack of basic knowledge of the condition was displayed by nurses or other staff who asked women who had AIS questions, such as "When was your last period or Pap test?"

Such encounters precipitate embarrassment and shame that is accompanied by a perceived stigma. Kitzinger [23] wrote: "The hushed conversations, the embarrassment of doctors, the explanations which don't add up, lead women and girls with AIS to the belief that they have a defect so monstrous that nobody is willing to discuss it."

Gender: acceptance and rejection

Although the three Ss—secrecy, shame, and stigma—were the most frequent psychiatric concerns with which our respondents had to deal, one of the most personal concerns is how the individual comes to deal with the apparent disparity of being girls or women who have an XY karyotype and testes. Persons who have AIS that live as boys or males do not have that concern, but do have to deal with breast development, sparse facial and body hair, and infertility.

All persons who have CAIS that were reared as girls live as women and identify as such. Adjustment to such an assignment was reported to be satisfactory by many investigators [24,25]. We also found that all of our respondents who had the complete syndrome lived as women and believed that it was the best

decision for them; however, this was not a simple solution for all. Other investigators also found that a significant number of women expressed reservations [26]. Acceptance of assignment does not mean that assignment has been correct. It just means that most are able to adapt and live with the handicap; however, they might have preferred other options [27,28]. We asked our 39 subjects who had CAIS to respond to published statements that were taken from ALIAS, an AIS newsletter.

The first statement was: "I don't think I am any different in feeling than if I were born XX...feel very female." Most (32 of 39; 82%) agreed with the statement but 7 (18%) women did not.

Another statement that was presented to the respondents was: "All my efforts over the years in presenting a female persona have left me completely exhausted. I might just as well have had a mastectomy, cut my hair short and lived as a celibate man. It would actually have been easier I think." Thirty-five (90%) subjects said that they disagreed with the statement.

When asked if they had to "work at being a woman," 17 (44%) of the respondents said that they "never" had to work at being a woman. The remaining 22 (56%), however, believed that at least some of the time this was something that they had to do. Twelve of the 22 believed that they must work at being female much of the time. The "working at" might have involved dressing in a feminine way or using cosmetics or hair styles in a way to signal "female" unambiguously. Some modified preferred behaviors, like altering their selection of clothes. Not uncommonly, there were expressions of difficulty and depression in having to overcome the knowledge that they were born XY and with testes; however, most believed that they eventually came to terms with the knowledge of their biology. There also were expressions of having missed typical "rites of female passage," such as menses and pregnancy.

Thirty-three (85%) patients in our group were content that they had been gonadectomized; they were aware that tumor formation was a potentiality. Reasons for discontent differed. One woman had an older sister who has AIS and is living satisfactorily with her testes, another believed that she was more self-confident before the surgery which only "confirmed" that there was something "wrong" with her, and a third would have preferred watchful waiting. A fourth believed that the resulting scars required too many difficult explanations.

Generally, satisfaction with their situation was different among those who had the partial condition. Those with PAIS often were ambivalent about their assigned gender. Most (67%) believed that the gender in which they were raised was best for them, whereas the others voiced reservations.

Most significant is the number of persons who, on their own initiative, shifted from their gender of rearing. Among our population of 18 subjects who had PAIS, 8 persons were raised as boys; 4 of these switched to live as woman before our investigation. Ten members of our population who had PAIS were raised as girls; 2 decided to live as men. Thus, 6 of 18 (33%) individuals were assigned to a gender that they rejected later. In 5 of these 6 individuals, the PAIS condition was confirmed by DNA or genital fibroblast examination [29]. The sixth indi-

vidual was unaware of which confirming tests were used, but, while living as a teenage girl, had been used in a medical school as an "example" of an individual who had PAIS.[2]

We recognized four subgroups among those who had PAIS. The first two subgroups were formed from the 10 subjects who had been raised as girls; one group continued on to live as women (n = 8; 80%), whereas the other group had decided to live as men (n = 2; 20%). The other two subgroups were formed from the 8 subjects who were reared as boys; one subgroups consisted of the 4 who continued to live as men and the other subgroup was made up of the 4 who decided to live as women.

Before making the gender switch, each person evaluated many personal and social considerations. The mean age at the shift in gender was 33.2 years (range 18 to 46). Of the two persons who switched from living as girls to live as men, one did so at 18 years of age and the other did it at age 30. Both of these individuals had married as women in attempts to conform to their gender of assignment and solidify their acceptance as women. Now, both of these men are angry that they were brought up as girls and are particularly bothered that, without their knowledge or informed consent, they were castrated and subjected to vaginal reconstructive surgery and from puberty on were given estrogens to feminize them somatically.

On the other side of the spectrum is one respondent who was raised as a boy but who now is living as a woman. For religious and other reasons she hesitated to change gender, although she had believed since childhood that it would be better to live as a female. Without being consulted, from the age of 11 to 13 she had four surgical procedures to masculinize her genitalia. She was drafted for the army, and without full medical/genetic examination, had been told that she had KS. As an adult–still living as a man–she married a woman in an effort to meet social expectations. Eventually, in her 40s, she developed testicular cancer and believed that because she required genital surgery, it would be an appropriate time to have genital reconstruction to regain her closed vagina, get divorced, switch gender, and, henceforth, to live as a woman. Later in life, a new clinician challenged her original diagnosis and ordered a DNA analysis for AIS, which confirmed that she had PAIS and was 46,XY.

Another case is instructive. An individual who is now living as a woman had been assigned as a girl at birth but was switched by a physician to live as a boy at the age of 3 months when testes were discovered. At the age of 13, her physician recommended that "he" have a mastectomy for his breast development. The surgery was performed and this individual continued to live as a boy although she had felt from early childhood that she would be more comfortable living as a girl. At the age of 22, she felt that she could not continue to live as a man

[2] Even if this person is omitted from consideration among our PAIS group, the number of those who switched from their gender of rearing is still a significant minority.

and switched to living as a woman when she learned that she could obtain breast implants to regain what had been removed.[3]

Presently, 12 (66%) of our PAIS sample are living as women and 6 (33%) are living as men. Among these 6 are 4 men who were raised as boys. They originally were assigned as girls but were switched by physicians to live as boys when inguinal testes were found at the ages of 6 years, 5 years, 18 months, and 2 weeks. Of these 4 subjects, the one who was reassigned at 18 months of age changed to live as a woman at the age of 34. The other 3 subjects continue to live as men. These 3 men married; 2 of them claimed that they will not shift from their present life as married men. One acknowledged that one of his younger siblings who also was raised as a boy did shift to live as a girl. He acknowledged that many of his behaviors and characteristics are considered effeminate and wishes that he could have larger male genitals to please his partner. He writes: "I have lived (more than 50 years) as a man now. For the last 5 years, I get more and more doubts as to what I am really. [But] I don't have any thoughts about changing to a woman." He doesn't want to lose his wife and adopted family and change his status.

Reports have been published about persons who had PAIS switching gender, accepting their gender assignment, or having difficulty in establishing a gender [28,30–32]. Preves [32] noted that the high prevalence in gender shift among the intersexed persons that she interviewed might have been influenced by the high educational level of her respondents. Schober [33] found that 8 of 10 subjects that she interviewed preferred being identified as intersexual, rather than as male or female, and that 2 of the 10 were undergoing sex reassignment; she believed that their undergoing reassignment or identifying as intersexed might be related to their educational attainment. The education of our respondents also might have been a factor in the gender change; all of those who switched gender had completed college or were working on, or had attained, a graduate degree. This also was true of those subjects in the group who had CAIS who were most critical of their status. Obviously, general and specific knowledge and interpretation of one's situation, as well as concepts of opportunity, can modify a person's life-altering decisions.

Psychologically relevant responses

In a standardized format, we asked our population who had AIS, "What do you feel are the most significant features of CAIS or PAIS with which

[3] This individual, while a teenager, was written up in a medical journal as an individual who had PAIS who accepted the male gender of rearing. She now claims that she never was asked searching questions about her own true gender preferences, never was informed fully of her medical condition, and never was told or believed that she had an option to change. Although this woman has remained in contact with the physician who wrote the paper more than 30 years ago, the physician has never written a follow-up publication revealing the rejected male role. This subject requested that we do not identify her in any way, including giving the citation for the publication in which she was mentioned originally.

you have to deal"? Frequent and common responses were variations of the following themes:

Secrecy, shame, and stigma
Being different in general
Concerns with infertility
Identity
How to resolve personal questions of masculinity and femininity.

We also asked our respondents "What are the most important points that need to be understood by someone with AIS"? The most common themes mentioned were:

There is more to sex and gender than chromosomal determination; gender identity (appearance in society) is not synonymous with sexual identity (biologic knowledge)
One who has AIS is not a freak; the condition is not something of which to be ashamed
Being a woman or man is a mental and physical process
Typical family life with marriage and adopted children is possible
Freedom of choice is crucial in the management of one's condition
One is not alone; support groups and the medical community can help

Lastly, is our finding that among our study population, 24 (62%) of those who had CAIS had considered suicide and 9 (23%) had attempted it. Among those who had PAIS, 11 (61%) had considered suicide and 3 (17%) had attempted it. The three who had attempted suicide did so before switching from their sex of rearing. Frequently, these considerations and attempts were associated with learning of their diagnosis or a problem with a specific amorous relationship.

Klinefelter's syndrome

KS is the most common sex chromosome disorder; some studies have found a prevalence of 1 or 2 cases/1000 population [34]. The original signal case was reported on an individual who had a 47,XXY karyotype [35]. Since then, the syndrome has come to include several genetic conditions in which there is an increased number of sex chromosomes. The sex chromosome complement can vary from the most typical, 47, XXY, to XXXY, XYY, XXYY, and other combinations, and, may occur with, or independent of, different mosaic conditions [36]. Individuals who have an XXX karyotype are considered to have a Klinefelter's variant by some investigators, although no Y chromosome is present. The presence of a Y chromosome usually leads to development as a male; persons who have XXX appear as females. Cases of individuals who had an XXY karyotype and a female phenotype have been reported [37].

Although KS is a genetic condition, there is no evidence it is inherited or familial [38]. Most commonly, the syndrome develops from a nondisjunction during a meiotic or mitotic phase [39]. These problems occur more frequently with increased maternal age [40]. In 1997, about 10% of KS cases were detected prenatally [41]. With increasing use of amniocentesis in older, pregnant women, these numbers can be expected to increase.

Physical features

The clinical features of KS are extremely variable. More frequently than those who have AIS, individuals who have KS may not be diagnosed until being worked up for infertility, hypogonadism, or other concerns. Because many individuals who have an XXY karyotype never develop the typical symptoms of KS, some researchers do not label someone as having KS unless prominent symptoms develop [42].

The most consistent basic features of KS include a male phenotype with hypogonadism, reduced or absent spermatogenesis, and increased levels of follicle-stimulating hormone [6]. Smyth and Bremner [38] stated that the variability in presentation is related mainly to the timing and amount of androgen deficiency. They and others investigators [43], recommended that school-age boys should have their testes palpated as part of a complete physical examination; those who seem to have learning difficulties or troubles with their peers should receive special attention.

The more supernumerary sex chromosomes that exist, the more likely are detrimental physical and mental findings [44]. Occasionally, a finding of cryptorchidism leads to a diagnosis of an XXY child because the karyotype is three times more frequent in this group than in the overall population [45].

One of the largest long-term studies of its kind, the so-called "Edinburgh study" [46], found that, at birth, babies who had KS generally were smaller in weight, length, and head circumference than were controls. The head circumference difference remained between the 10th and 25th percentiles and reflected an adverse effect on brain growth [47]. A notable increase in height velocity occurred between the ages of 5 and 8 years of age because of the greater leg growth; however, the typical pubertal growth spurt did not differ from controls. A tendency to central obesity was seen in 75% of the XXY boys who were followed.

A minority of the XXY infants in the Edinburgh study was born with small penises that prompted treatment with localized testosterone cream. These treatments were successful in stimulating penis growth; however, by the end of puberty, the penis was of normal size in only 77% of the boys [46]. In contrast, the testes were normal in size at birth but failed to grow normally.

Gynecomastia in KS, is seen in from 30% to 90% of patients [44,48]. Some reports indicate that breast development will be minimal and of little consequence [42], whereas other investigators report that the gynecomastia will persist [35,49]. In general, long-lasting and prominent gynecomastia does not regress as a result of androgen treatment but might do so in less obvious cases [6]. Gyne-

comastia often is a source of great shame to the teen-age boy [50]. Reduction of psychologically-disturbing breast growth can be accomplished by surgery or liposuction. The incidence of breast carcinoma is significantly greater than in the typical male [51].

Prepubertal boys who have KS tend to be taller than average with a disproportionate leg length [52]. The onset of puberty can occur normally or be delayed [53]. Following puberty, along with gynecomastia, there may be diminished body and facial hair, a female pubic hair pattern, small phallus, poor muscular development, and progressive disproportion in leg and body length. Feminine fat distribution around the hips and abdomen is noted [38].

The presence of a normal XY cell pattern, along with KS lines, usually modifies the expression of the syndrome so that these patients usually are diagnosed later, display a lesser degree of gynecomastia, and show fewer feminine characteristics and less testicular pathology [54]. Fertility becomes increasingly doubtful as age advances; however, before infertility is predicted, sperm analysis is required because paternity has been documented [55].

Learning considerations

Referral to child psychiatrists often occurs as a result of concern with schooling or behavior. Males and females who have alterations in sex chromosome number are at increased risk for behavioral and learning disabilities [56]. Theilgaard [48], however, reports that the Wechsler Adult Intelligence Scale (WAIS) IQ range of those who have XXY or XYY is large and includes scores that are in the normal and superior ranges.

Specific reading deficits have been reported in 50% of children who have KS [57]. Generally, there seem to be a mild delay in language acquisition [58] and depressed motor development [59].

Often, boys who are affected with KS are shy, passive, quiet, immature, and dependent [59]. Typically, intelligence scores are lower than those of their siblings and tend to reflect lower verbal skills [49]. Because many men who have KS are never diagnosed, it is difficult to estimate or quantitatively document the frequency or the severity of the intellectual and psychologic problems. In addition, there seems to be considerable variability in this area; many affected males clearly have above-average intellect [48].

Comparing XYYs and XXYs with respect to their projective test results does not show marked differences, with the exception of sex role. "The XXY's have more problems with their masculine role, appear less masculine, and are more submissive and dependent than XYY's. In their drawings they also show less sex-differentiation. The defensive patterns vary, the XYY's being more evasive, and the XXY's showing more denial...[but] the similarities far outweigh the differences" [48].

Minor deviations in motor, speech, and emotional development suggest a common underlying pattern of altered development that may become apparent during early childhood, before the onset of the classic physical features of the

syndrome. If recognized, in many cases the problems can be alleviated through appropriate intervention [43]. Such management can include specific academic schooling, attention to speech and hearing problems, and emotional support [42,60].

Personality considerations

In general, XXY boys as toddlers, frequently are seen as shy and reserved, easy to manage, and adaptable [60]. Parents often describe low levels of activity. During school age, many are described as timid, introverted, quiet, cooperative, eager to please, and well-liked by their teachers [61]. They also have been described as passive, nonassertive, and not as active as their peers [59]. In the Edinburgh study, 47% of the boys who had KS were referred for psychiatric assistance compared with 9% of the male controls. Teacher or parental complaints were in regard to temper tantrums, antisocial activities, and enuresis [47]. Differences in temperament were found between those who had XXY and those who had XYY. The former are more likely to be bullied by others, whereas those who have XYY are more likely to be the bullies [48].

During adolescence and transition through puberty, boys who had KS showed low self-esteem, anger, frustration, or depression. [62]. They reported less sexual interest in girls and had a significantly later onset of masturbation. The number who did masturbate and the frequency of masturbation was not, however, different between the KS and control groups [63]. High School Personality Tests of XXY boys found them "more tender minded, sensitive, apprehensive, self-reproaching, and insecure, while on the Bem Sex Role Inventory they had significantly lower scores on the masculinity scale...less interest in girls, to date less, to have less sexual experience, and to be less socially involved" [64]. Boys who had KS also were likely to view themselves lower on a masculinity scale [65].

Theilgaard [48] found, after considering all aspects of overall psychologic functioning, that the XXY and XYY groups were more alike than different. Significant differences were noted, however, in expressed sexual interest and activity. Those who had XYY masturbated more frequently in childhood and adulthood, express less guilt, were younger at first intercourse, had more partners, and reported higher libido and more unconventional sexual activities than those who were XXY. In the "Draw A Person Test," those who had XXY draw more differentiated images; those who had XYY drew elaborate "overdimensionalized sexual attributes."

The lack of masculine sense is seen from childhood in boys who have XXY but from puberty in boys who have XYY [48]. A Danish study compared 34 men who had XXY who were older than 20 years of age with 16 men who had XYY; it was noted that those who were XXY had lower libido and significantly fewer had engaged in sexual intercourse [66]. Similar findings were reported by other investigators [67]. These types of differences seem to persist. Raboch et al [68] reported that, among men who had KS—86% of whom were married at the time—"Subjects with Klinefelter's syndrome date later...kiss for the first time

later. . .attempt initial intercourse later and actually perform it later. . .Furthermore they have intercourse with a second partner later. . .and the number of their coital partners is fewer. . .chromatin positive men belatedly fall in love for the first time and start a long-lasting love affair at a later age."

Gender expression

Infrequently discussed in medical descriptions of KS are individuals' concerns with gender expressions and feelings. An unknown percentage of persons who have KS experience androgynous or feminine feelings that can develop at an early age [50]. Some people who have KS consider themselves to be transgendered [50], others considered themselves to be intersexed [69], and others considered themselves to be transsexual.

One of the most noted persons who transitioned gender is Carolyn Cossey, a "James Bond girl." She was raised as a boy, but changed to live as a girl at a young age, and became a famous model; her karyotype was found to be XXXY [70].

Wyler et al [71] found that two of nine candidates that they recommended for transsexual surgery and female hormones had KS. A host of investigators similarly reported cases of men who had KS who transitioned to live as women or who harbored aspects of gender dysphoria [72–74]. Walzer and Hurwitz [75] concluded that all of the KS patients that they saw viewed their personalities as dual male and female and wrote: "Investigators periodically report they can find no increase in sexual deviancy in patients with a chromosomal abnormality. Only too often the methods used to ascertain the presence of such a deviation. . .are not conducive to discovering it." We know of two relevant cases; one is a mathematics professor who underwent sex reassignment surgery to live as a woman and a previous medical student who is presently in the process of transition. The frequency of gender change in KS is unknown.

Several papers have commented that homosexuality among those who had KS was not found among their subjects [46] or that the prevalence was not any different from that seen in the general population [42].

Treatment and recommendations regarding androgen insensitivity syndrome and Klinefelter's syndrome

Recently, KS received attention in an attempt to derive new research priorities and stimulate investigation in this area of intersexuality [76]. New reviews of this condition, along with focus on AIS, are welcome.

AIS and KS benefit from many similar treatments and recommendations. Children and adolescents who have intersex conditions deserve, and benefit from, appropriate psychiatric care and counseling. The diagnosing physician should encourage such attention, even if it is not requested by the patient or parent. Therapy should be age-appropriate, honest, and open with sensitivity to intersex issues. Psychiatric care in an empathic setting is preferable to concealment or

self-discovery in an environment that is devoid of support [77]; support should be ongoing as necessary.

Goodall [78] advised that children do not view their troubles as adults do; attempts to protect them from adult knowledge may leave them vulnerable to a shocking revelation at exactly the age when conformity with peers and sexual identity are important and also could breed noncompliance with treatment. "A better approach is to unfold the truth state by stage, matching simple statements to the child's conceptual growth until the personal implications are finally realized as part of a maturing process." [78]. Bock [42] reminds us that "when the truth is withheld, children often suspect that their parents are hiding something and may imagine a condition that is worse than their actual diagnosis."

Simultaneous with informing the patient or parents about the diagnosis and discussing medical concerns, there should be adequate opportunity for questions and debate. Contact with a particularly aware individual who has a similar condition or to a support group is advocated.[4] Those who have AIS or KS and their parents have found such associations to be helpful.

Parental counseling can start as soon as the child's condition is determined and can precede counseling of the child [27,79,80]. The type and magnitude of this assistance depends on the individual child, the specific condition, and the parent's own resources—psychologically, socially, and otherwise [34].

Specific aspects of psychotherapy that need attention are the items that were identified above in the AIS section; these are applicable to patients who have KS. Counseling should, in addition, cover concerns with body appearance and physiology, relationships among peers and potential sexual partners [81], genetics [82], and sexual functioning.

Those who have AIS or KS and live as girls or women have to reconcile that they are living with an anomalous karyotype, are born with testes, will not menstruate, and will be infertile; they will miss many of the social milestones of the typical female. Those who have AIS or KS and live as boys or men need to deal with breast development and other physical differences from their peers and the knowledge that they probably will be infertile. Although most boys and girls have no difficulty in resolving questions of gender, all have to deal with associated considerations. Some will choose to live in a gender other than that in which they were reared; generally, this will not be easy. Manifestations of effeminacy or masculinity in contrast with their chosen gender is a topic that often will need to be addressed. Teenage boys and girls are particularly sensitive about how their peers perceive them and how well they integrate with them.

For those who are dealing with gender issues, Hoffman [83] advised that therapists assist the patient to challenge disturbing stereotypes of masculinity and

[4] When not convenient geographically, support groups are available by way of the Internet. Some AIS groups limit themselves to those who live as women although a few groups welcome men as well. Some groups are led by parents and others are directed by intersexed individuals.

femininity and to explore how the individual learned to be a boy or girl. It also is helpful to offer basic information about genital developmental processes and distinguishing sex from gender [84] and to keep in mind that concepts of gender are culturally based [85]. If gender change is considered appropriate, support is crucial.

Among those persons who have AIS and live as women, vaginal enlargement is an issue that often needs to be addressed. Surgical intervention has been challenged, particularly when it is done without the informed consent of the patient [86]. Gooren [87] wrote: "Dilation is the intervention of first choice. It is self-performed, using a progressively enlarged series of penis-shaped dilators. . .Gentle pressure is applied into the vaginal outlet, and over the course of several weeks or longer a 10-minute period of dilation twice a day may suffice. Psychological counseling is needed during this period as there may be a phobia of vaginal penetration or the girls may equate the procedure with masturbation, particularly when the dilator is obtained from a nonclinical source." Moen [88] also found that self-dilation and cautious intercourse was effective in enlarging the vagina. Parents should be consulted and counseled about these practices because they might have their own questions and concerns regarding its timing and other ramifications. Appropriate counseling regarding vaginal functioning should be ongoing [31].

Advice regarding testosterone or dihydrotestosterone (DHT) administration to those who have AIS and live as men, as well as those who have KS, varies and is based on little experimental data. The value of androgens for those who have AIS probably is related to the exact nature of the mutation that is involved [89] because it helps a few people but not most. In large dosages, testosterone was successful in producing significant phallic growth and enhancing male living [90]. DHT was helpful in restoring male genital development in an infant who had PAIS [91]. For individuals who have been gonadectomized, as well as those who have KS, hormonal management helps to prevent osteoporosis and other medical conditions.

For undermasculinized boys or men who have KS, Nielsen and colleagues [66,92] and Forest [4] recommended testosterone treatment that was started early in puberty. They claimed that it helped to prevent the development of deviations in behavior and learning abilities at school. Testosterone also was noted to stimulate and increase general activity and well-being. Treatment of KS with testosterone is suggested, beginning at 11 to 12 years in accord with the patient's state of well-being, degree of virilization, and growth [44]. In general, parenteral androgens were more effective in inducing virilization and were safer than oral preparations [6].

How individuals respond to their intersex conditions varies greatly. From the varieties of findings in the accumulated reports, it should not be anticipated that a person who has AIS or KS will fit any model or demonstrate any particular personality characteristics. Stereotyping those who have AIS or KS into homogeneous profiles should be resisted. As in other aspects of medicine, children and adolescents need to be dealt with as individuals.

References

[1] Uehara S, Tamura M, Nata M, Kanetaki J, Hashiyada M, Terada Y. Complete androgen insensitivity in a 47,XXY patient with uniparental disomy for the X chromosome. Am J Med Genet 1999;86:107–11.

[2] Quigley CA, De Bellis A, Marschke KB, El-Awady MK, Wilson EM, French FS. Androgen receptor defects: historical, clinical and molecular perspectives. Endocr Rev 1995;16(3): 271–321.

[3] Gottlieb B, Pinsky L, Beitel LK, Trifiro M. Androgen insensitivity. Am J Med Genet 1999; 89(4):210–7.

[4] Forest MG. Diagnosis and treatment of disorders of sexual development. In: DeGroot LJ, Jameson JL, editors. Endocrinology, vol. 3. 4th edition. Philadelphia: W. B. Saunders Company; 2001. p. 1974–2010.

[5] Imperato-McGinley J, Zhu Y-S. Gender and behavior in subjects with genetic defects in male sexual differentiation. In: Pfaff DW, Arthur PA, Etgen AM, Fahrbach SE, Rubin RT, editors. Hormones, brain and behavior, vol. 5. San Diego (CA): Academic Press; 2002. p. 303–46.

[6] Grumbach MM, Huges IA, Conte FA. Disorders of sex differentiation. In: Kronenberg HM, Melmed S, Polonsky KS, editors. Williams textbook of endocrinology. Philadelphia: W. B. Saunders; 2003. p. 842–1002.

[7] Gottlieb B, Beitel LK, Lumbroso R, Pinsky L, Trifiro M. Update of the androgen receptor gene mutations database. Hum Mutat 1999;14(2):103–14.

[8] Batch JA, Patterson MN, Hughes LA. Androgen insensitivity syndrome. Reprod Med Rev 1992;1:131–50.

[9] McEwen BS. Gonadal steroid influences on brain development and sexual differentiation. In: Greep RO, editor. Reproductive physiology IV, international review of physiology, vol. 27. Baltimore (MD): University Park Press; 1983. p. 99–145.

[10] Hines M. Sexual differentiation of human brain and behavior. In: Pfaff DW, Arthur PA, Etgen AM, Fahrbach SE, Rubin RT, editors. Hormones, brain and behavior, vol. 4. San Diego (CA): Academic Press; 2002. p. 425–62.

[11] Quigley CA, Friedman KJ, Johnson A, Lafreniere RG, Silverman LM, Lubahn DB, et al. Complete deletion of the androgen receptor gene: definition of the null phenotype of the androgen insensitivity syndrome and determination of carrier status. J Clin Endocrinol Metab 1992; 74(4):927–33.

[12] Evans BAJ. Phenotypic diversity in siblings with partial androgen insensitivity syndrome. Arch Dis Child 1997;76:529–31.

[13] Viner RM, Tech Y, Brown BD, Patterson MN, Hughes IA. Androgen insensitivity syndrome: a survey of diagnostic procedures and management in the UK. Arch Dis Child 1997;77(4):305–9.

[14] Kessler SJ. Lessons from the intersexed. New Brunswick (NJ): Rutgers University Press; 1998.

[15] Anonymous. Once a dark secret. Br Med J 1994;308:542.

[16] Natarajan A. Medical ethics and truth-telling in the case of androgen insensitivity syndrome. Can Med Assoc J 1996;154:568–70.

[17] Groveman SA. The Hanukkah bush: ethical implications in the clinical management of intersex. J Clin Ethics 1998;9(4):356–9.

[18] Kemp BD, Groveman SA, Anonymous, Tylo HD, Irwin KM, Natarajan A, et al. Sex, lies and androgen insensitivity syndrome. Can Med Assoc J 1996;154(12): 1829–33.

[19] Warne GL. The baby of uncertain sex. Pediatr Surg 1992;7:244–8.

[20] Diamond M. Pediatric management of ambiguous and traumatized genitalia. J Urol 1999;162: 1021–8.

[21] Liao LM. Learning to assist women born with atypical genitalia: journey through ignorance, taboo and dilemma. J Reprod Infant Psychol 2003;21(3):229–38.

[22] Wilson BE. Androgen insensitivity syndrome. Available at: www.emedicine.com/PED/topic2222.htm. Accessed March 4, 2003.

[23] Kitzinger C. Women with androgen insensitivity syndrome. In: Ussher JM, editor. Women's health. Leicester (UK): British Psychological Society; 2000. p. 387–94.
[24] Wisniewski AB, Migeon CJ, Meyer-Bahlburg HF, Gearhart JP, Berkovitz GD, Brown TR, et al. Complete androgen insensitivity syndrome: long-term medical, surgical, and psychosexual outcome. J Clin Endocrinol Metab 2000;85(8):2664–9.
[25] Hines M, Ahmed SF, Hughes IA. Psychological outcome and gender-related development in complete androgen insensitivity syndrome. Arch Sex Behav 2003;32(2):93–101.
[26] Migeon CJ, Wisniewski AB, Gearhart JP, Meyer-Bahlburg HFL, Rock JA, Brown TR, et al. Ambiguous genitalia with perineoscrotal hypospadias in 46,XY Individuals: long-term medical, surgical, and psychosexual outcome. Pediatrics 2002;110(3):616–21.
[27] Diamond M, Sigmundson HK. Management of intersexuality: guidelines for dealing with persons with ambiguous genitalia. Arch Pediatr Adolesc Med 1997;151:1046–50.
[28] Kuhnle U, Krahl W. The impact of culture on sex assignment and gender development and gender development in intersex patients. Perspect Biol Med 2002;45(1):85–103.
[29] Edelstein RA, Carr MC, Caesar R, Young M, Atala A, Freeman MR. Detection of human rogen receptor mRNA expression abnormalities by competitive PCR. DNA Cell Biol 1994; 13(3):265–73.
[30] Gooren LJG, Cohen-Kettenis PT. Development of male gender identity/role and a sexual orientation towards women in a 46,XY subject with an incomplete form of the androgen insensitivity syndrome. Arch Sex Behav 1991;20(5):459–70.
[31] Vates TS, Fleming P, Leleszi JP, Barthold JS, Gonzalez R, Peelmutter AD. Functional, social, and psychological adjustment after vaginal reconstruction. J Urol 1999;162:182–7.
[32] Preves SE. Negotiating the constraints of gender binarism: intersexuals' challenge to gender categorization. Curr Soc 2000;48(3):27–50.
[33] Schober JM. Sexual behaviors, sexual orientation and gender identity in adult intersexuals: a pilot study. J Urol 2001;165(6 part 2):2350–3.
[34] Nielsen J, Wohlert M. Sex chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Birth Defects Orig Artic Ser 1991; 26:209–23.
[35] Kleinfelter HRJ, Reifenstein ECJ, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydism, and increased excretion of follicle-stimulating hormone. J Clin Endocrinol 1942;2:615–27.
[36] Mandoki MW, Sumner GS, Hoffman RP, Riconda DL. A review of Klinefelters syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1991;30(2):167–72.
[37] Schmid M, Guttenbach M, Endres H, Terruhn V. A 47,XXY female with unusual genitalia. Hum Genet 1992;90:346–9.
[38] Smyth C, Bremner WJ. Klinefelter syndrome. Arch Intern Med 1998;158:1309–14.
[39] Abruzzo M, Hassold TJ. Etiology of nondisjunction in humans. Environ Mol Mutagen 1995; 25(Suppl 26):38–47.
[40] Carotheres AD, Fillippi G. Klinefelter's syndrome in Sardinia and Scotland: comparative studies of parental age and other aetiological factors in 47,XXY. Hum Genet 1988;81:71–5.
[41] Abramsky L, Chapple J. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis with implications for prenatal counseling. Prenatal Diagnoses 1997;17:363–8.
[42] Bock R. A guide for XXY males and their families. Available at: http://www.nichd.nih.gov/publications/pubs/klinefelter.htm. Accessed August 11, 2003.
[43] Battin J, Malpuech G, Nivelon JL, Garandeau P, Freycon F, Sultan C, et al. Le syndrome de Klinefelter en 1993. Resultats d'une enquete multicentrique sur cinquante-huit cas et revue de la literature. [Klinefelter syndrome in 1993. Results of a multicenter study on 58 cases and review of the literature]. Ann Pediatr (Paris) 1993;40(7):432–7 [in French].
[44] Chen H. Klinefelter syndrome. Available at: http://www.emedicine.com/PED/topic1252.htm. Accessed August 11, 2003

[45] Topper E, Doickerman Z, Prager-Lewin R, Kaufman H, Maimon Z, Laron Z. Puberty in 24 patients with Klinefelter syndrome. Eur J Pediatr 1982;139:8–12.
[46] Ratcliffe S. Long term outcome in children of sex chromosome abnormalities. Arch Dis Child 1999;80(2):192–5.
[47] Ratcliffe SG, Masera N, Pan H, Mckie M. Head circumference and IQ of children with sex chromosome abnormalities. Dev Med Child Neurol Suppl 1994;36:533–44.
[48] Theilgaard A. A psychological study of the personalities of XYY and XXY men: assessment and discussion. Acta Psychiatr Scand 1984;69(Suppl 315):70–124.
[49] Ratcliffe S, Bancroft J, Axworthy D, McLaren W. Klinefelter's syndrome in adolescence. Arch Dis Child 1982;57:6–12.
[50] McKinlay IW. The KS Story: You are not alone. Peebles, Scotland, in press.
[51] Hultborn R, Hanson C, Kopf I, Verbiene I, Warnharmmas R, Weimarck A. Prevalence of Klinefelter's syndrome in male breast cancer patients. Anticancer Res 1997;17:4293–7.
[52] Schibler D, Brook CG, Kind HP, Zachmann M, Prader A. Growth and body proportions in 54 boys and men with Klinefelter's syndrome. Helv Paediatr Acta 1974;29:325–33.
[53] Berenguer B, de la Cruz L, de la Plaza R. The role of lipoaspiration in defeminization of Klinefelter syndrome: a case report. Ann Plast Surg 1999;43:306–8.
[54] Theilgaard A. A psychological study of the personalities of XYY and XXY men. Acta Psychiatr Scand 1984;69(Suppl 315):14–5.
[55] Laron Z, Dickman Z, Zamir R, Galatzer A. Paternity in Klinefelter's syndrome–a case report. Arch Androl 1982;8(2):149–51.
[56] Geschwind DH, Boone KB, Miller BL, Swerdloff RS. Neurobehavioral phenotype of Klinefelter syndrome. Ment Retard Dev Disabil Res Rev 2000;6:107–16.
[57] Graham J, Bashir A, Stark R, Silbert A, Walzer S. Oral and written language abilities of XXY boys: Implications for anticipatory guidance. Pediatrics 1988;81:795–806.
[58] Rovet J, Netley C, Keenan M, Bailey J, Stewart D. The psychoeducational profile of boys with Klinefelter syndrome. J Learn Disab 1996;29:180–96.
[59] Nielsen J, Sorensen AM, Sorensen K. Follow-up until age 7 to 11 of 25 children with sex chromosome abnormalities. Birth Defects Orig Artic Ser 1982;18(4):61–97.
[60] Walzer S, Bashir AS, Silbert AR. Cognitive and behavioral factors in the learning disabilities of 47, XXY and 47, XYY boys. Birth Defects Orig Artic Ser 1991;26(4):45–58.
[61] Walzer S, Bashir Jr A, Graham Jr JM, Silbert AR, Lange NT, DeNapoli MF, et al. Behavioral development of boys with X chromosome aneuploidy: Impact of reactive style on the educational interventions for learning deficits. Birth Defects Orig Artic Ser 1986;22:1–21.
[62] Bender BG, Harmon R, Linden M. Psychosocial adaptation of 39 adolescents with sex chromosome abnormalities. Pediatrics 1995;96:302–8.
[63] Bancroft J, Axworth D, Ratcliffe S. The personality and psycho-sexual development of boys with 47 XXY chromosome constitution. J Child Psychol Psychiatry 1982;23:169–80.
[64] Roy A. Psychiatric disorders in relation to Klinefelter's syndrome. In: Bandmann E-J, Breit R, Perwein E, editors. Klinefelter's syndrome. Berlin: Springer-Verlag; 1984. p. 192–201.
[65] Martinius J. Psychiatric aspects of Klinefelter's syndrome in adolescence. Klinefelter's syndrome. Heidelberg, Germany: Springer-Verlag; 1984.
[66] Nielsen J, Johnsen S, Sorensen K. Follow-up 10 years later of 34 Klinefelter males with karyotype 47,XXY and 16 hypogonadal males with karyotype 46 XY. Psychol Med 1980;10: 345–52.
[67] Sorensen K. Physical and mental development of adolescent males with Klinefelter syndrome. Horm Res 1992;37(Suppl 3):55–61.
[68] Raboch J, Mellan J, Starka L. Klinefelter's syndrome: sexual development and activity. Arch Sex Behav 1979;8:333–9.
[69] Butler J. Groom's intersex quandary. The West Australian Saturday 2002;5.
[70] Cossey C. My story. London: Faber and Faber; 1991.
[71] Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. Der transsexualismus und dessen

therapie. Transsexualism and its therapy. Schweiz Arch Neurol Neurochir Psychiatr 1979; 124(1):43–58 [in German].
[72] Baker HJ, Stoller RJ. Can a biological force contribute to gender identity? Am J Psychiatry 1968;124(12):1653–8.
[73] Seifert D, Windgassen K. Transsexual development of a patient with Klinefelter's syndrome. Psychopathology 1995;28(6):312–6.
[74] Parks JS. Cognitive style and gender role in persons with sex chromosome aberrations. Hosp Pract 1977;12(10):93–102, 107–8.
[75] Walzer S, Hurwitz I. Psychosexual ambiguity in Klinefelter's syndrome. Semin Psychiatry 1970; 2(1):53–64.
[76] Simpson JL, de la Cruz F, Swerdloff RS, Samango-Sprouse CS, Kakkebaek NE, Graham JMJ, et al. Klinefelter syndrome: expanding the phenotype and identifying new research directions. Genet Med 2003;5:460–8.
[77] Pinsky L, Trifiro M. Androgen insensitivity syndrome. Gene reviews. Available at: http://www.geneclinics.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=6jQCCNiJukpy4&gry=&fcn=y&fw=gC1J&filename=/profiles/androgen/index.html. Accessed on March 27, 2004.
[78] Goodall J. Helping a child to understand her own testicular feminization. The Lancet 1991; 337(8732):33–5.
[79] McGillivray BC. Genetic aspects of ambiguous genitalia. Pediatr Clin North Am 1992;39(2): 307–17.
[80] Slijper FME, Drop SLS, Molenaar JC, Scholtmeijer RJ. Neonates with abnormal genital development assigned the female sex: parent counseling. J Sex Educ Ther 1994;20(1):9–17.
[81] Efthim PW, Kenny ME, Mahalik JR. Gender role stress in relation to shame, guilt, and externalization. J Couns Dev 2001;79:430–8.
[82] Drop SL, Boehmer AL, Slijper FM, Nijman JM, Hazebroek FW, Niermeijer MF. Differential diagnosis and treatment of girls with 46XY-karyotype and androgen insensitivity syndrome. Ned Milit Geneeskd Tijdschr 2001;145(14):665–9.
[83] Hoffman RM. The measurement of masculinity and femininity: historical perspective and implications for counseling. J Couns Dev 2001;79:472–85.
[84] Diamond M. Sex and gender are different: sexual identity and gender identity are different. Clin Child Psychol Psychiatry 2002;7(3):320–34.
[85] Kuhnle U, Krahl W. The impact of culture on sex assignment and gender development in intersex patients. Perspect Biol Med 2002;45(1):85–103.
[86] Beh HG, Diamond M. An emerging ethical and medical dilemma: should physicians perform sex assignment surgery on infants with ambiguous genitalia? Mich J Gend Law 2000;7(1):1–63.
[87] Gooren LJG. Androgen-resistance syndromes: considerations of gender assignment. In: Bardin CW, editor. Current therapy in endocrinology and metabolism. 6th edition. St. Louis (MO): Mosby; 1997. p. 380–4.
[88] Moen MH. Creation of a vagina by repeated coital dilatation in four teenagers with vaginal agenesis. Acta Obstet Gynecol Scand 2000;79(2):149–50.
[89] Weidermann W, Peters B, Romalo G, Spindler K-D, Schweikert H-U. Response to androgen treatment in a patient with partial androgen insensitivity and a mutation in the deoxyribonucleic acid-binding domain of the androgen receptor. J Clin Endocrinol Metab 1998;83(4):1173–6.
[90] Grino PB, Isidro-Gutierrez RF, Griffin JE, Wilson JD. Androgen resistance associated with a qualitative abnormality of the androgen receptor and responsive to high-dose androgen therapy. J Clin Endocrinol Metab 1989;68:578–84.
[91] Ong YC, Wong HB, Adaikan G, Yong EL. Directed pharmacological therapy of ambiguous genitalia due to an androgen receptor mutation. The Lancet 1999;354:1444–5.
[92] Nielsen J, Pelsen B, Sorensen K. Follow-up of 30 Klinefelter males treated with testosterone. Clin Genet 1988;33:262–9.