CASE SUMMARY

A 46,XY individual born with a stretched penis length of 1.5 cm was reassigned female at 5 months of life. Risks of female reassignment were discussed; parents signed a detailed hand-written consent. Testes were removed, and the penis was refashioned as a clitoris. With Figs 1–5, we provide a chronological summary in which we detail the life events for this 39-year-old well-adjusted man. Despite multiple genital surgeries and a long-term commitment to a female patient, male gender by parents and caregivers, gender adjustment problems developed, and at age 29 years, after full medical history disclosure, this patient self-reassigned as male. This patient is now a self-supporting, socially active, married, sexually active, unequivocal heterosexual man.

abstract

This report of a 46,XY patient born with a micropenis consistent with etiology from isolated congenital growth hormone deficiency is used to (1) raise the question regarding what degree testicular testosterone exposure to the central nervous system during fetal life and early infancy has on the development of male gender identity, regardless of gender of rearing; (2) suggest the obligatory nature of timely full disclosure of medical history; (3) emphasize that virtually all 46,XY infants with functional testes and a micropenis should be initially boys except some with partial androgen insensitivity syndrome; and (4) highlight the sustaining value of a positive long-term relationship with a trusted physician (R.M.B.). When this infant presented, it was commonly considered inappropriate to gender assign an infant male whose penis was so small that an adult size was expected to be inadequate, even if the karyotype was 46,XY, and testes were functional. Concomitantly, female gender assignment was considered the appropriate decision, believing that parental rearing in the assigned gender was considered the major factor determining established adult gender identity. Full disclosure of medical information was considered inappropriate. Progress in appreciating the complexities of gender identity development, which is not yet completely understood, and sexuality, coping ability, and outcome data has resulted in a change of practice in initial gender assignment. A 46,XY individual with functional testes and verified androgen responsiveness should be assigned and reared as male, regardless of penis size. Without androgen responsiveness, the multiple factors must be carefully considered and disclosed.
that a struggle with female gender began during childhood). With Figs 1 and 2, we outline the medical history; genital anatomy; gender assignment; growth hormone (GH) testing; pregonadectomy hypothalamic–pituitary–testicular function; the dramatic fivefold phallic growth from 6 mm to 3 cm during GH therapy; behavioral, psychological, functional difficulties; and recurrent problems from previous genital surgery. Concerns involved genital differences compared with other girls (again perhaps this signals that a struggle with female gender began during childhood), and clitoral erections. The patient delayed the recommended onset of estrogen therapy for several years (further evidence of a struggle with female gender), beginning sex steroids at age 11.5 years with vaginoplasty at 14 years. Concerns included an atypical reproductive anatomy, noncompliance with estrogen therapy (sign of a gender struggle) and prescribed vaginal dilation, and desire for sexual hair (Fig 3). In early adulthood, during a 3-year interval without physician contact, the patient worked as a nursing assistant, refused hormones and/or medications, declared herself “lesbian” (although sexual orientation itself is not evidence of incorrect gender assignment, this may indicate a struggle with female gender), and related and identified with other similar-aged lesbians (Fig 4). At 22, she reestablished physician contact and indicated that she had previously told doctors what she thought they wanted to hear, rather than how she felt. She still refused hormonal therapy (indication of not wanting female characteristics), was gender-neutral in appearance, and began requesting full medical history and records. As was common in this era, records had not been made available consistent with the perception that disclosure might foster more psychological problems.

Finally, at age 29, her medical history was reviewed and explained by R.M.B. over several sessions (Fig 5). This disclosure was followed by an immediate gender change to male similar to a case in which a person with a diagnosis of partial androgen insensitivity syndrome (pAIS) changed gender from male to female upon learning of her medical history.1 Mastectomy was undertaken, and testosterone therapy was initiated. After full replacement was achieved, orgasmic ability was restored. GH deficiency was reverified, and adult GH replacement therapy was begun. His birth certificate was reissued male. Now, multiple years after these changes, this man continues to be gainfully employed, is socially active, maintains fulfilling relationships with family and friends, has enjoyed physical intimacy, including 2 long-term romantic relationships with women that included male-typical sexual activities (with the inherent limitations imposed by penile absence), and by his mid-30s was married. This may imply that, although fetal testosterone was insufficient to stimulate fetal penis growth in the face of GH deficiency, testosterone exposure to the central nervous system (CNS)
The family moved back to the former state, growth on GH therapy continued along the 50th percentile, and estradiol therapy was offered whenever the patient wanted to begin wearing a bra, but was declined. Among the many factors he feels fostered his positive adjustment, he cites his and his family’s long-term relationship with his pediatric endocrinologist (R.M.B.) as the most important and supportive. Case reports, such as this one, in which the influence of medical, hormonal, psychological, and cultural mediating factors are highlighted can be used to provide valuable information, in part to respond to justify criticism by patients and advocates that poor psychosocial and sexual outcomes may be less a function of atypical sex hormone exposure or surgical procedures and more a consequence of the complex interplay between multiple experiences (eg, having chronic condition and attendant experiences, reaction of parents, medical decision-making, lack of disclosure and feelings of secrecy and shame, and effects of possible peer rejection) that modulate the outcomes within and across developmental stages. Although excellent progress has been made in our management of these patients, our understanding of the biological and social factors that contribute to healthy psychosocial development remain an area of uncertainty, particularly in how individual personality factors, such as resilience, influence outcomes. It is still true that this type of variability in behavioral outcomes makes a perfect gender assignment impossible in all cases. With this current case report, we point to the need for cautious and careful case-by-case management for these patients and, when possible, for such management to be performed by open-minded multidisciplinary teams.

Etiologies of micropenis commonly include pituitary gonadotropin deficiency, androgen biosynthetic defects, and PAlS. Classic teaching is used to instruct us that fetal and neonatal penis growth is primarily driven by androgen stimulation (via dihydrotestosterone). Isolated GH deficiency is typically not mentioned as a cause of micropenis, although penis growth has been reported among patients with GH deficiency who received GH therapy. Authors of textbook chapters may mention isolated GH deficiency as a possible etiology of micropenis but without specific case citation. Thus, this case represents the first published report of isolated congenital GH deficiency causing micropenis, and, with it, we demonstrate the impressive phallic growth noted after GH therapy and highlight this as a treatable etiology. However, GH treatment does not guarantee that adult penis size will be in the normal range or that psychological challenges and dissatisfaction will not occur.
during the first 1.5 years of GH therapy). This patient, with no other anterior pituitary hormone deficiencies, demonstrated dramatic growth of the phallic corpora from nonpalpable to 3.0 cm during the first 1.5 years of GH therapy. The genital surgery precluded not only the documentation of the impact of short-term growth response to GH in a small penis as a consequence of GH deficiency but also made it impossible to speculate whether a normal adult size would have been reached with long-term GH therapy.

Although penile growth acceleration is obvious during periods of androgen treatment, there is no evidence that testosterone treatment before puberty increases the eventual size of the adult penis. As is seen in human growth in stature, adult penis size in those with a micropenis cannot always be specifically predicted because of the multiple factors involved; however, some outcome data reveal that adult penis length can be within 2 SD of normal in patients without GH deficiency born with a micropenis.

Hence, depending on etiology of congenital micropenis, penis growth potential cannot be easily predicted at presentation and may be greater than initially forecasted; this is an effect first noted in gonadotropin deficiency and by way of the data presented in this case in those with GH deficiency. Outcome data are even less clear and are perplexing for those with PAIS, ovotesticular disorders of sex development (DSD), and testicular agenesis or regression syndrome.

A female assignment was long considered the ultimate alternative in patients with a micropenis with a forecasted penile growth expected to be well below the normal adult range. This was based on the rationale that a penis of "sufficient" size was a significant factor in the well-being of a man (on the basis of proposed benefits of standing to urinate, for traditional penetrative intercourse, and the unverified implication that penis size is an index of masculinity). From the surgical standpoint, it was also naively considered more feasible to create a penetrative conduit than a penetrating organ. The gradual trend away from female assignment in patients with 46,XY DSD during the last 2 decades, particularly in those with less severe undervirilization, has resulted in higher rates of male gender assignments for individuals with 46,XY DSD during the last 2 decades, particularly in those with less severe undervirilization. In addition, dramatic refinement of surgical techniques for masculinizing genitoplasty have also occurred over the same interval. However, because long-term health and quality of life outcomes of such changes are not available for at least 2 decades, further systematic confirmation of the benefits of these shifts remain. It is critical to point out that the ethical dilemmas involved in medical and surgical management of persons with congenital atypical genital development will persist regardless of improved surgical techniques or cosmetic outcomes, because surgery is not the primary driver of outcome in these cases but should be considered complementary to a thoughtful initial gender management and is maximally beneficial when it aligns with the future adult sexual identity.

With this case, we suggest that, in addition to prenatal testosterone CNS exposure, the presence of a
46,XY karyotype may also be a factor in the development of a male gender identity. Because gender identity is a complex construct involving multiple components, many additional factors should be considered when trying to understand the reasons for self-reassignment of gender. Empirical evidence of the extent of influence exerted by prenatal testosterone on gender identity remains inconclusive, with more definitive evidence for testosterone’s role in gender role interests and behavior and, recently, in influencing sexual attraction toward women. Although, with this case report, we provide evidence used to reinforce the role of androgen (and functioning androgen receptors) in influencing masculine-typical brain and gender identity development, any significant role of an XY karyotype on sexual development, although intuitive, remains speculative. For example, 46, XY women with complete androgen insensitivity syndrome show brain responses to sexual images similar to 46,XX women and markedly different from XY men, with whom they share a Y chromosome and a high prenatal and infant testosterone secretion. Those with complete androgen insensitivity syndrome lack functional androgen receptors, which precludes a cellular response to testosterone; however, testosterone is readily aromatized to estradiol resulting in normal feminization at puberty, via normally functioning estrogen receptors. With these findings and our current report, we suggest multivariate contributions to gender-specific brain development while emphasizing the importance of both nature and nurture. Prenatal gonadal hormonal exposure, as well as exposure during early infancy and puberty may provide additional sensitive periods when sex steroids are able to influence human neurobehavioral organization. Sex-linked genes could also contribute to sex-related variability in brain development or responses to certain hormonal stimulus, and socialization is known to heavily influence many sex-related behavioral characteristics.

Nevertheless, with this case, we strongly support rearing 46,XY infants with functional testes, a normal androgen receptor, and micropenis as male, regardless of penis size. Among those with pAIS, only those patients who fail to demonstrate phallic growth after exogenous testosterone should be considered for female assignment. Although there are not good criteria for a normal phallic response (a general rule has been a 100% increase in penis length), clinically, a positive response is unequivocally apparent by inspection. Outcome data for those with pAIS include individuals who self-initiated gender change in both directions. This highlights the lack of data used to provide guidance on which gender to initially assign among these infants, beyond the general principle that lack of physical (genital) response to testosterone may also indicate lack of responsiveness in other organs such as the CNS, hence a lack of whatever effect androgen has to impart male gender development. With this case, we also highlight the perils of the previous management paradigm in which the assertion was made that initial gender assignment, when associated with consistent rearing and psychosocial input from others, would establish a desired gender identity regardless of etiology.

The current approach to these patients is outlined in a recent publication and reflects the shift from female assignment in any 46, XY individual. Authors of a recent summary do not mention the possibility of female assignment, whereas those of another publication only note the controversy of such. Researchers of outcome data regarding gender issues, body image, social fitness, sexuality, work, family adjustment, and psychopathology suggest that men born with a micropenis have similar outcomes to men in control groups in these domains. This, of course, should not imply that 46,XY individuals with a micropenis reared as male do not experience psychosexual and psychosocial problems. Satisfactory genitosexual function was found among those reared as male, but extensive feminizing surgery was associated with a negative outcome for those reared as female. With this report, we found that, regardless of the initial assignment, the majority of patients indicated satisfaction with their assigned gender and showed similar degrees of dissatisfaction with genital appearance and function, leading to the conclusion that male assignment is preferable because genital surgery is not needed. These results must be taken within the context that studies on psychosexual development and psychosocial well-being in men with DSD or other genital atypicality are rare, and, as in the studies cited above, the authors of such studies include only a small number of participants, with large numbers of potential participants declining participation, such that conclusions should be interpreted with caution.

In this case, adequate penile length, or even having a penis, was not shown to be a prerequisite for a man to have successful sexual contact; this would appear to be a consequence of an adjustment to face reality. This coping mechanism is similar to that reported for a group of men with small penises who also seemed to have learned to de-emphasize the importance of intercourse and had found alternative ways for themselves and their partners to pleasure each other and reach orgasms. In other reports, however, when small penis size persists into adulthood it was a major cause of dissatisfaction. This can be interpreted to mean that, generally,
penis size matters, particularly if an individual focuses on this and lacks the affirmation that, for this as well as other situations in life that cannot be altered, accepting this fact and de-emphasizing its importance is the only reasonable way forward. The challenge for both parents and health professionals is how to help such a person develop the kind of resilience demonstrated by the person in this report.

During several instances beginning during childhood, there were signals (noted above), that this person was struggling with the assigned female gender. It was full education and disclosure regarding her DSD condition and treatment that provided the knowledge to make sense of what she had been struggling with for years (the assigned female gender). This confirmed the conviction that she had a male gender identity. Although routine psychological “checkups” were generally not done or available, this evidence also would suggest that, if these had occurred, this person may have been spared years of distress and uncertainty. Fortunately, R.M.B. was able to provide this vital educational history within the context of a 35-year relationship with this patient and his family. Unfortunately, such physician-patient relationships are not common today. The questions are, “At what age should information be given?” and “How should the information be imparted?” The issue is no longer whether to disclose the information but when and how to tell it. It has been shown that informing children of their condition is beneficial.\textsuperscript{26} Generally, information should be given in small increments at different times. For the mature child, the oldest appropriate age to begin would be just before puberty or during puberty. For years, parents, despite fears, agreed that their children had the right to know the full details of their DSD condition and treatment and that the information should be given in stages.\textsuperscript{27} Such a step-by-step approach was suggested\textsuperscript{28} and, today, there are many educational resources, some for specific DSD conditions, for children, adolescents, and young adults (eg, www.acordalliance.org). This link also has a list of support groups by specific DSD condition.

It has become clear that best practice must include psychosocial management that is not only used to focus on gender development and sexually related aspects of care but also other quality of life domains. This approach, referred to as a noncategorical approach,\textsuperscript{29} views DSD as a chronic condition similar to other pediatric conditions. This model of care is patient and family focused and emphasizes that quality of life encompasses many aspects of development.

The purpose of such protocol-driven psychological monitoring is to (1) establish rapport (an essential component of successful counseling); (2) assess normal domains of development for age, including gender identity; (3) address issues relevant to developmental age; (4) provide education about endocrine conditions by answering questions and concerns; (5) provide a setting to reiterate what has been learned about condition, medications, etc; (6) begin sex education relevant to development age to be used as a template on which to place patients’ DSD; (7) discuss romantic and sexual interests, fears, etc; (8) introduce the topic of DSD support groups; and (9) provide opportunities to meet others with similar conditions. Although the noncategorical approach follows a generic protocol, it recognizes that the patient and family come first and that flexibility along with long-term monitoring and rapport are key assets to best practice. The goal of both medical and psychological care via an interdisciplinary team is a person who is well adjusted in the face of unchangeable physical characteristics.

**Abbreviations**

CNS: central nervous system
DSD: disorders of sex development
GH: growth hormone
pAIS: partial androgen insensitivity syndrome

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