Male Gender Identity in an XX Individual with Congenital Adrenal Hyperplasia

Juan Carlos Jorge, PhD,* Carolina Echeverri, BS,† Yailis Medina, BS,† and Pedro Acevedo, BS†

*Department of Anatomy and Neurobiology, School of Medicine, University of Puerto Rico, San Juan, Puerto Rico; †School of Medicine, University of Puerto Rico, San Juan, Puerto Rico

DOI: 10.1111/j.1743-6109.2007.00558.x

ABSTRACT

Introduction. In spite of significant changes in the management policies of intersexuality, clinical evidence show that not all pubertal or adult individuals live according to the assigned sex during infancy.

Aim. The purpose of this study was to analyze the clinical management of an individual diagnosed as a female pseudohermaphrodite with congenital adrenal hyperplasia (CAH) simple virilizing form four decades ago but who currently lives as a monogamous heterosexual male.

Methods. We studied the clinical files spanning from 1965 to 1991 of an intersex individual. In addition, we conducted a magnetic resonance imaging (MRI) study of the abdominoplevic cavity and a series of interviews using the oral history method.

Main Outcome Measures. Our analysis is based on the clinical evidence that led to the CAH diagnosis in the 1960s in light of recent clinical testing to confirm such diagnosis.

Results. Analysis of reported values for 17-ketosteroids, 17-hydroxycorticosteroids, from 24-hour urine samples during an 8-year period showed poor adrenal suppression in spite of adherence to treatment. A recent MRI study confirmed the presence of hyperplastic adrenal glands as well as the presence of a prepubertal uterus. Semistructured interviews with the individual confirmed a life history consistent with a male gender identity.

Conclusions. Although the American Academy of Pediatrics recommends that XX intersex individuals with CAH should be assigned to the female sex, this practice harms some individuals as they may self-identify as males. In the absence of comorbid psychiatric factors, the discrepancy between infant sex assignment and gender identity later in life underlines the need for a reexamination of current standards of care for individuals diagnosed with CAH. Jorge JC, Echeverri C, Medina Y, and Acevedo P. Male gender identity in an xx individual with congenital adrenal hyperplasia. J Sex Med 2008;5:122–131.

Key Words. Congenital Adrenal Hyperplasia; Gender Identity; Intersexuality

Introduction

Genital ambiguity at birth, a virilized female, or an undervirilized male, may be indicative of a series of conditions related to intersexuality [1–3]. An intersex individual is one who is born with genitalia and/or secondary sex characteristics that cannot be classified exclusively as male nor female, or which combine features of the male and female sexes. There is no consensus in the literature with regard to prevalence estimates for intersex births [4,5]. Nevertheless, the American National Organization of Rare Disorders (http://www.rarediseases.org/, accessed on April 11, 2007) lists several intersex phenotypes as rare or “orphan” diseases under different categories. It has been estimated that between 0.1% and 0.2% of live births are ambiguous enough to become the subject of specialist medical attention, including surgery to adjust their genital appearance to

Congenital adrenal hyperplasia (CAH) underlies their sex assignment [1]. The management of children with intersex conditions has been the subject of debate among the medical and legal fields for at least 50 years [6,7]. One of the fundamental issues at stake is the practice of sex assignment or sex reassignment during a developmental period where gender identity is not apparent.

In recent years, there has been a significant shift in management policies with regard to sex assignment or reassignment of intersex infants [8–10]. The “optimal gender policy” by John Money and the Hampsons in the 1950s proposed that humans are born psychosexually neutral, and that the sex of rearing plays a pivotal role in gender identity formation. They proposed that a clinical decision regarding sex assignment should take place prior to the second year of life and that children should not become aware of their sex history in order to avoid psychological distress and/or doubts about the assigned sex [11,12]. An important shift in the clinical management of these cases is full disclosure of medical information to the affected parents and their participation in the decision-making process, a paradigm that is known as “full consent policy” [6,13–16]. In order to unify a set of criteria for the clinical management of intersex individuals, the Committee of Genetics and the sections of Endocrinology and Urology of the American Academy of Pediatrics continues to recommend genital surgeries after full discussion of clinical information to the parents [17]. In spite of this shift, several advocacy groups including the Intersex Society of North America (http://www.isna.org/, accessed on April 11, 2007), the Peer Support for Intercourses in Japan (formerly Hijra Nippon; http://home3.highway.ne.jp/pesfis/, accessed on April 11, 2007), and the UK Intersex Society (http://www.ukia.co.uk/, accessed on April 11, 2007) propose a moratorium to infant genitoplasties following sex assignment and to allow individuals to decide their own sexual identity [18]. However, this proposition is not attainable in light of the societal mandate to assign sex shortly after birth. In addition, this proposition is inconsistent with current standards of care for these individuals. Colombia is the only Western society where the courts can participate in the decision-making process for infant sex assignment based on their constitutional law [19,20].

Congenital adrenal hyperplasia (CAH) underlies the intersex phenotype in approximately 80% of the cases [21] and is the only one that may indicate an underlying life-threatening metabolic problem. CAH involves a series of autosomal recessive disorders that involve the complete or partial deficiency of an enzyme involved in the synthesis of cortisol and/or aldosterone. The most common type of CAH is due to 21-hydroxylase deficiency (for a review, see [22]). Standard work-up procedures to diagnose CAH types 1-IV include karyotype testing, identification of Mullerian structures by magnetic resonance imaging (MRI) and/or ultrasound, and assessment of 17-OH progesterone levels in plasma [23]. It has been the standard practice to assign the female sex to individuals with an XX karyotype and associated pelvic structures in spite of significant virilization of their sexual organs [24]. However, a percentage of CAH females are not satisfied with their female sex assignment and prefer to live as males [22]. The discrepancy between the clinical management of CAH females and their self-identification as females or males underlines the need for a better understanding on the complex interactions between the biology of sex, gender identity, gender role, and sexual orientation (for a review, see [25]). Gender identity is a person’s self-recognition as either male or female [22]. Gender role is the social expression of an individual’s gender identity (for a review, see [26]). Females with CAH recall having boy-like play behaviors during their childhood. Parents of females with CAH also described their children as tomboyish [27,28]. Lastly, sexual orientation refers to a person’s erotic interest in male or female sexual partners. Zucker et al. [28] reported that there is no difference between female CAH and their non-CAH female relatives with regard to their relationship status (married/cohabitation vs. single) and sexual preferences. In contrast, Long et al. [29] found that CAH females have a lower frequency of partner affiliations and sexual activities than their unaffected relatives, and a higher rate of homosexual desires and/or relationships.

In this study, we present the case of an intersex individual whose sex assignment at birth was male but was reassigned to female after a team of doctors diagnosed the infant as a female pseudohermaphrodite with CAH simple virilizing form at 20 months of age. This individual currently lives as an adult heterosexual male in Puerto Rico. We used the individual’s clinical records spanning from 1965 to 1991; we conducted a series of semistructured interviews with the oral history method, and we presented data from a recent MRI study of the abdominopelvic anatomy of the individual to understand his/her self-identification as a male in spite of a clinical sex reassignment to the female sex. The case is presented in the historical

J Sex Med 2008;5:122–131
framework and current standards of care for intersex conditions.

**Consent for Publication**

In 2004, Juan/Ana asked the corresponding author of this report (J.C. Jorge) to make public his/her clinical and personal history. In order to protect the ethical and legal matters involved in the disclosure of clinical information in this particular case, both parties signed an agreement establishing that the information will be used for research purposes and that the real identity of the individual will always be kept anonymous. Interviews were recorded digitally and files were kept with a numerical code. Clinical files were provided by Juan/Ana with the approval of his/her legal representatives. Files were reviewed by the four authors only. Authors signed a document agreeing not to disclose the identity of Juan/Ana. Another document was fashioned stating that all parties agree with this report as it appears in this journal in its final form. Copies of these three documents are under the custody of Juan’s/Ana’s legal representatives and the corresponding author.

**Results**

The individual was born during the 1960s, the ninth child of 11 pregnancies, in a small town in the mountains of Puerto Rico. This individual was assigned to the male sex at birth; in this report, we used the name “Juan” to refer to the individual’s identity at this stage of his/her life history. The mother noticed that the baby showed distress during voiding. Physical exams and tests led to the diagnosis of ambiguous genitalia and a definitive sex assignment as a female, with Prader 3 genitalia ([30], Figure 1). Physicians requested the court to change the name and sex of the infant in the birth certificate; in this report, we used the name “Ana” to refer to the individual’s identity at this stage of his/her life history. After further testing, clinicians reached a final diagnosis of female pseudohermaphroditism with CAH, simple virilizing form. Figure 2 shows the hormonal biosynthetic pathway that is compromised in this condition.

The clinical approach that led to the CAH diagnosis in the university hospital setting where this case was managed during the mid 1960s included two 24-hour urine samples to assess levels of 17-ketosteroids (17-KS), buccal smear and peripheral blood sample for karyotype testing, physical examination of the external genitalia, intravenous pyelogram, and hysterogram. Figure 3 shows the reported levels of 17-KS and 17-hydroxycorticosteroids (17-HS) while on cortisone acetate treatment. As can be seen, 17-KS and 17-HS remained high for most part of the treatment. Figure 4 shows 17-KS levels during treatment with cortisone acetate, dexamethasone, prednisone, or hydrocortisone from 0 to 8 years of age. Analysis reveals poor adrenal suppression in spite of treatment. During separate interviews with the mother, she confirmed full compliance with the prescribed treatment for adrenal suppression. She reported that the pediatric endocrinologist warned her that her child could die if she failed to follow treatment. Nevertheless, in spite of adherence to
treatment and poor adrenal suppression, Juan/Ana was consistent with his/her desire to dress and to behave like a boy throughout childhood.

By age 5, Juan/Ana was not aware of his/her condition and genital status. The patient only came to understand the peculiarity of his/her genitalia by comparing with the anatomical appearance of his/her peers. After years of tomboyish behavior and precocious sexual encounters with girls, the patient reached his/her preteen years to confront a clitoridectomy and vaginoplasty, as follow-up procedures from a previous surgical vaginal opening and plastic repair of the clitoris. Table 1 summarizes the clinical approaches to manage this CAH individual. After various statements of the patient’s identity as a male, the endocrinologist requested a psychological evaluation. Male gender identity was confirmed as recalled by the individual; however, a record of this fact could not be found in the clinical records. By age 11, genital surgery was performed successfully. However, the individual was incompliant with vaginal dilation rendering surgery as an incomplete procedure.

Although we found many instances in the clinical records referring to a series of vaginal bleedings reported as menses, these were most likely associ-
ated with genitoplasties. Figure 5 shows the results of a recent MRI study where an infantile uterus is apparent, as that of a female who has never had her menses. By his/her early 20s, the patient decided to change his/her appearance for that of a man. Following a clinical note from 1992 that reported the presence of enlarged adrenal glands, and the cessation of medication 11 years prior to this date, we were interested in investigating the patient’s present status with respect to the adrenal glands. Adrenal enlargement is a common feature in patients with CAH, usually with poor to no adrenal suppression. MRI testing showed enlarged adrenals with 2- and 4-cm tumorlike multiple formations on the right and left adrenals, respectively (Figure 6). Previous clinical notes revealed the presence of a normal uterus, vaginal canal, and no ovaries, as these were removed when Juan/Ana, at age 20, considered a phalloplasty to conform to his/her male identity. The patient later decided not to undergo surgery even though a full 2-day psychiatric evaluation approved it. According to the clinical notes, the specialist concluded that Juan/Ana is a male and not an intersex individual with gender identity disorder. We conducted a series of interviews with the patient using the oral history method. A resilient theme in the interviews was the patient’s sexual experiences since early childhood. Recall of games during childhood was consistent with a male gender identity. In descending order, the five most frequent games reported during interviews were wrestling, biking, mom and

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965–1982</td>
<td>Glucocorticoids and mineralocorticoids</td>
</tr>
<tr>
<td>December 1966</td>
<td>Incision of urogenital sinus</td>
</tr>
<tr>
<td>January 1967</td>
<td>Vaginoplasty and plastic repair of clitoris</td>
</tr>
<tr>
<td>December 1976</td>
<td>Vaginoplasty and resection of clitoris</td>
</tr>
<tr>
<td>1981</td>
<td>Vaginoplasty</td>
</tr>
<tr>
<td>1992</td>
<td>Psychiatric evaluation</td>
</tr>
</tbody>
</table>

Figure 4 Levels of 17-ketosteroids (17-KS) associated to the administration of different glucocorticoids. The horizontal line represents the normal range of 0–1 mg/d at which 17-KS levels typical for a 0- to 8-year-old child. Notice that only 3 out of 46 values are within the normal range. Two of these were regulated with cortisol acetate and one with dexamethasone. Cortisone acetate was the glucocorticoid administered after age 8. Data were taken from the clinical records of the patient.

Figure 5 Pelvic magnetic resonance imaging (MRI) study. MRI revealed an infantile uterus and patent vaginal canal. No ovaries were identified. Study was performed at 39 years of age.

J Sex Med 2008;5:122–131
dad role play where Juan/Ana played the dad role always, playing with truck toys, and basketball.

Juan/Ana and his/her female partner met at the workplace 15 years ago. Juan/Ana disclosed his/her clinical history early on during their friendship. The female partner had two boys from a previous relationship at the time that they met. Juan/Ana was a father figure to them and a grandfather to their children. The reported sexual repertoire by Juan/Ana and her partner is typical for heterosexual encounters, and the penis was substituted with sex toys. They had never engaged in gender-bending games during sexual arousal, and the female partner had never penetrated Juan/Ana. The female partner considered herself a monogamous heterosexual female. Juan/Ana had been her second sex partner during her life history. Juan/Ana obtained a college degree in a medical field and ran a successful business with his/her partner. For the past decade, Juan/Ana had been trying to regain his/her legal identity as a male without success.

Discussion

Intersex individuals have been treated in different ways by different cultures [3,31–33]. Since the rise of modern medical science, Western societies have required that they conform to one sex. However, there are increasing calls for recognition of the various degrees of intersexuality as healthy variations, which should not be subject to genital normalizing surgery [4,18,34]. In fact, corrective surgery is generally not necessary for the protection of life or health, but purely for aesthetic and/or social purposes. The Juan/Ana case is yet another clear example of how the clinical management of intersexuality failed to create an individual satisfied with his/her assigned sex. Although this is now a common finding, the social concerns and the limitations brought by government laws makes sexual assignment and genital normalizing surgery a priority in these cases. As it has been a common experience for intersex patients from previous decades, the family of this individual was not informed about the etiology and available treatments for CAH. When clinicians recommended genital normalizing surgeries as part of the clinical management, the rural family agreed to it, thinking it was part of a medical emergency pertinent to their child’s CAH condition. One can only expect that this clinical approach to manage CAH no longer takes place in the 21st century [7]. The “full consent policy,” the guidelines provided by the American Academy of Pediatrics with regard to the management of intersexuality in 2000 [17], and the public awareness raised by several intersex advocacy groups aim to protect the well-being and the legal rights of these individuals in society. The full consent policy is intended to guarantee the full disclosure of clinical information and full participation of parents in the decision-making process during sex assignment. In contrast, the “optimal gender policy” has been intended to avoid psychological ambiguity and to minimize social pressures with regard to the desirability of parents to enforce the sex that the clinical team decides is best suited for their child. In addition to this significant advance in the field, experts have noted that the Internet and patient-driven advocacy groups have been effective at raising concerns regarding the clinical management of intersexuality [8,16]. It is worth noting that the Internet and advocacy groups were not alternatives for patients when the optimal gender policy was widely adopted by
Several experts in the field have argued that the unsexiness with the female sex assignment among some CAH patients may stem from three different aspects: late female sex assignment, late genital plastic surgery, and/or inadequate suppression of the adrenal glands. It is clear that these three factors are present in the clinical history of Juan/Ana. The first two factors correlate with a theory developed in the 1950s by Dr. John Money and the Hampsons [11,12] and developed further by Money and Ehrhardt in the 1970s who established the hypothesis that humans are born with what they called “psychosexual neutrality” [35]. This leads to the conclusion that an individual can be reared as either male or female, despite their chromosomal or gonadal sex if assigned before 2 years of age. This hypothesis was tested in the infamous John/Joan case. However, in the 1990s, Drs. Diamond and Sigmundson revised the John/Joan case, and brought to light the psychological turmoil that the patient suffered because of the gender assignment during infancy. They established that even when social upbringing is important, the prenatal androgen exposure may play a role in gender identity formation [14].

Although it has not been clearly established that gender identity is determined by chromosomal sex, sex of rearing, or prenatal hormone exposure, androgens constitute a common ground for researchers and clinicians to argue about male gender identity among XX individuals. The debate is based on a wealth of animal research showing that exposure to androgens affects the sexual differentiation of the brain and behavior. To this date, it is yet unclear whether prenatal, postnatal, or perinatal androgen environments play a role, if any, in establishing gender identity. However, it is becoming increasingly clear that androgens play a strong modulatory role on adult female sexual behaviors [36-38]. Nevertheless, the precise mechanism(s) underlying gender identity formation in children is/are unknown ([10]; for a review, see [26]). However, because the sexual differentiation of the brain occurs during the first 5 years of life (for reviews, see [39,40]), it is likely that gender formation takes place during a developmental period and through mechanisms independent from those mediating the sexual differentiation of the external genitalia. The latter occurs during the first trimester of fetal life.

Hines [27] have shown a positive correlation between high testosterone levels in intrauterine environment and tomboyish behavior at the age of 3.5 years in non-CAH girls. But it has not been possible to establish a correlation between the degree of genital masculinization in terms of Prader stages or clitoral size as an indicator of brain masculinization. In fact, predictors of self-initiated gender change to male among CAH individuals have not been researched ([41]; for a review, see [25]). When considering gender identity and gender role, Meyer-Bahlburg [41] has noted that female to male change among CAH females may concur with an atypical body image and the development of an erotic desire toward women. As Juan/Ana reported, “...I am a boy, because I like girls...”, “...I’m a boy because I have something down there that girls do not have...” In addition, Juan/Ana showed tomboyish behavior throughout childhood, which caused alienation from peers and rejection, frustration, and discrimination by some members of his/her family. These life experiences most likely influenced the development of his/her gender identity even though he/she had to wear dresses, make up, heels, and remove facial hair with tweezers to please his/her mother. He/She also experienced aggression from his/her brother because of his belief that his sister was “butch”. It is not surprising that some intersex children show poor psychological adjustment in everyday life events [42].

Juan/Ana was submitted to a full psychiatric evaluation in the United States in the 1990s as he/she sought sex reassignment to male at the age of 20. That clinical report and our interviews confirmed an identity consistent with a male. We did not find any indicators for gender dysphoria or a comorbid psychiatric condition at any time during his/her life history. Interviews with his/her family and sex partner confirmed Juan/Ana’s psychological health. The only episode of depression followed a vaginolasty procedure at 11 years of age as specified in the medical records and in the psychiatric evaluation.

Traditionally, creating a fertile and a sexually functional woman has been the major criteria influencing decisions on sex assignment for XX individuals with CAH [17]. However, there has been a significant number of recent scientific advances in the field that make this unquestioned principle outdated. Advances in molecular endocrinology have shown the “XX male” [43] and the “XY female” [44] phenotypes, which should force us to examine our views on chromosomal sex. Similarly,
advances in reproductive technologies can now make possible management of full-term pregnancies after ovum transfer a matter of routine procedures. In addition, there is evidence for sex-specific gene activation before gonad formation demonstrating that our current understanding of the embryological processes that lead to sexual differentiation is, at best, incomplete [45]. It is also clear that, in spite of significant advances on genitoplasties, these procedures are still not perfect, have yet to become standard surgical techniques across the country, most procedures still require surgical revisions, and more importantly, there is a high incidence of dissatisfaction with regard to sexual function during adulthood [46–56].

Today, we are beginning to recognize non-transgender individuals who voluntarily seek orchidectomy to conform to their sexual identity [57,58]. But before them, society came to terms with the transsexual identity through their social and legal validation by medicine ([59]; for a review, see [60]). However, intersex individuals have yet to enjoy the same validation even though the first clinical photographs depicting a nontypical, but natural, sexual anatomy dates back to close to one and a half centuries ago [61].

Conclusion
Taken together, we conclude that, first, there are clinical cases that clearly defy our current algorithm of sex classification based on chromosomal makeup, the presence of pelvic Mullerian or Wolffian structures, and hormonal profiles; second, there is a need for long-term outcome studies on the management of CAH and on the clinical histories where CAH individuals self-initiate a change in gender identity; and last, as simple as it may sound, we have yet to understand why gender identity may not correlate with the appearance of the external genitalia. We must strive to fill this fundamental gap in the field before deciding the sex of an infant.

Acknowledgments
The authors thank Drs. John GH Cant and María Sosa-Llorens for their insightful comments of an earlier version of this article.

Corresponding Author: JC Jorge, PhD, School of Medicine—Anatomy, PO Box 365067 San Juan, Puerto Rico 00936-5067. Tel.: 787–758-2523, 1506; Fax: 787-767-0788; E-mail: jcjorge@rcm.upr.edu

Conflict of Interest: None declared.

Statement of Authorship
Category 1
(a) Conception and Design
JC Jorge
(b) Acquisition of Data
JC Jorge, C. Echeverri, Y. Medina, P. Acevedo
(c) Analysis and Interpretation of Data
JC Jorge, C. Echeverri, Y. Medina, P. Acevedo

Category 2
(a) Drafting the Article
JC Jorge, C. Echeverri, Y. Medina, P. Acevedo
(b) Revising It for Intellectual Content
JC Jorge, C. Echeverri, Y. Medina, P. Acevedo

Category 3
(a) Final Approval of the Completed Article
JC Jorge

References

J Sex Med 2008;5:122–131