REVIEW

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Extensive Literature Review of 46,XX Newborns with Congenital Adrenal Hyperplasia and Severe Genital Masculinization: Should They Be Assigned and Reared Male?

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Abstract

46,XX individuals born with severely masculinized genitals due to congenital adrenal hyperplasia (CAH) who have been assigned male at birth and reared male can successfully establish a male gender identity/role, find employment, marry, function sexually with a female partner, and develop positive mental health status. While there were a few individuals who reportedly did not fare well or who changed gender to female, the majority of those identifying as males appear to have an overall good quality of life. Parental/family support, along with the support of others, appears essential to a positive outcome as a male, or as a female. This paper suggests that serious consideration should be given to male gender assignment and rearing and, in certain situations, is justified. Disorders of sex differentiation teams should inform parents about the option for male assignment and rearing in 46,XX CAH infants with severe genital masculinization, which is a rare condition. To provide this option is concordant with the principles of ethics, transparency and with the Endocrine Society Guidelines and the American Academy of Pediatrics' policy of fully informed consent.

Keywords: Masculinized genitalia, congenital adrenal hyperplasia, gender, sexuality, 46,XX males

Introduction

Originally described in 1865 (1), the congenital adrenal hyperplasias (CAH) are autosomal recessive disorders characterized by impaired cortisol synthesis. The worldwide incidence is estimated to be from 1:14,000 to 1:18,000 births (2). Most cases (>95%) are the result of 21-hydroxylase deficiency caused by a mutation in the *CYP21A2* gene (3). There are two classic forms of CAH, salt wasting (SW) and simple virilizing. CAH occurs in both sexes with external genital masculinization occurring in females. The degree of masculinization is indicated by the Prader Scale (4) with the most severe masculinization being graded four or five. Five indicates a fully formed penis with the meatus at the tip and a fully formed but empty scrotum. Internally, in 46,XX patients the reproductive organs are female.

The goal of the Pediatric Endocrine Society (PES) in formulating treatment guidelines has always been female assignment of all 46,XX CAH infants as females to "… preserve functional anatomy and fertility (2)". The 2005 consensus statement recommended more outcome data regarding male gender assignment for severely masculinized newborns diagnosed with 46,XX CAH (5). It shuld be noted that this statement was not a recommendation against male assignment (6). Historically some such individuals were assigned male before the diagnosis was made.

The purpose of this article is to summarize the published psychosexual (gender identity, gender role, sexual orientation) and behavioral outcome of adult 46,XX CAH individuals initially assigned and reared as males. The second purpose is to present the pros and cons of full

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disclosure regarding male gender assignment among severely masculinized infants.

Methods

A systematic search of PubMed was performed using these key words: 46,XX CAH; adrenogenital syndrome; assigned male; reared male; Prader stage 4; Prader stage 5; gender identity; gender role/expression; sexual orientation; sexual function; and mental health. Inclusion criteria were: cases in English of 46,XX CAH adults; 17 years and older; and assigned male at birth because of extremely masculinized external genitalia. These cases provided outcome data on gender identity, gender role, sexual orientation, work, marriage, and mental health. Excluded case reports were those that described: [1] children who died in infancy; [2] males who were too young to provide outcome data; and [3] those who were initially assigned as male then reassigned female at an age too young to provide outcome data (6,7). Also excluded were reports with only aggregate data (8,9).

Patients identified from publications from PubMed search (n = 131)	→	Patients removed based on exclusion criteria n = 78	→	Patients retained by inclusion criteria n = 53 from 18 publications

The Results and Discussion sections are identified by the reference numbers and, when pertinent, case numbers.

Results

Accurate Diagnosis Delayed

Delay of diagnosis of 46,XX CAH is a hallmark of individuals born with 46,XX CAH with severely masculinized genitalia (Table 1). Delay ranged from 0.1 to 35 years. The median was 6.8 years, although given the range of years and dates of the included reports, this figure is less meaningful and we refer the reader to Table 1. Surprisingly, delay has been documented even with accurate diagnosis (10,11).

Penile Length

Seventeen measurements of stretched or erect penile length were found in seven reports, including two separate measurements on three patients (12, Case 1,2,3) and are shown in Figure 1, plotted on a normal distribution population graph (13) based on data from Schonfeld and Beebe (14). They are also found in Table 1. The median length was 6.5 cm. although this includes those who had endogenous or exogenous androgen exposure.

Gender Identity

Table 1 shows all 53 adults who were initially assigned males: 46 living/identifying as males; 4 living/identifying as females; and 3 reassigned to female but self-gender changed back to male. Hence, of the 53, 92% identify as male. Being male was firmly established in the only report using questionnaires assessing outcome in adult life (7). This is consistent with a report of three adult patients reared male, reporting happiness and satisfaction without regrets (12, Case 1, 2, 3). Similar responses are published for 18- (15, Case 1) and 26-year-old men (16, Case 1). Another case (17, Case 2) reported that parents and surgeon did not accept the sex reversal. The surgeon removed Mullerian structures but refused to remove the "large clitoris similar to adult phallus". At age 36, the case was short (147 cm/4 feet 9 inches), depressed, expressed regret and cannot find an "appropriate job" (17, Case 2). A case identified as "bi-gender" has had "hard social adjustment" (18, Case 4).

Four individuals were reassigned and continued to live as females. One person lived as a male until age four when a CAH diagnosis was made and 46,XX karyotype was found. Change was recommended because the "tiny" penis precluded a normal male sex life "whereas fertile life in the female sex was clearly possible". This individual was initially reported to have behaved "more or less like a normal boy" except sitting to urinate (19). At age 22, she married, being fully aware of her medical history and considered the error had been corrected. At age 26 she conceived and gave birth via Caesarean section (20). The second female was reared as a male until age 12 years when she was evaluated for breast development and vaginal bleeding. With the help of her parents, she accepted the recommended gender change "easily". She later married and had two biological children and is "satisfied with her gender" (17, Case 1). The third individual, reported at age 26 years, lived as a male until age 16 years when adrenal hyperplasia was diagnosed.

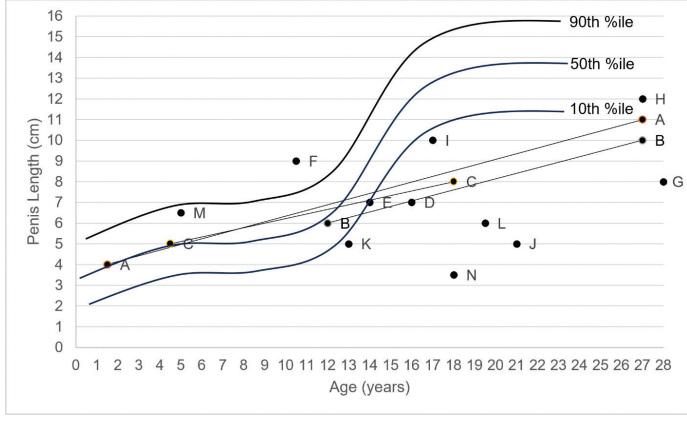

Figure 1. Penile growth graph

Table 1. CAH 46,XX adults (≥17 years) with severe virilization assigned male

Reference & country	Apóstolos et al. (12) (2018) Brazil			Bin-Abbas et al. (16) (2014) Saudia Arabia			Dewhurst and Gordon (19) (1984) USA	Gillenwater et al. (10) (1970) USA
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3		
Prader score	IV	V	IV	IV	V	V	V*	V
CAH diagnosis	SV 21-OH	SV 21-OH	SV 21-OH	CYP11B1 (Novel)	CYP11B1 (Novel)	CYP11B1 (Novel)	CAH	
Delay (years) 46,XX diagnosis	1.67	12	5	16	14	10	4	6
Age informed of diagnosis (years)				16	14	10		
Current age reported (years)	27	27	18	26	24	20	26	21
Gender change? (age in years)	No	No	No	Yes (17)	No	No	Yes (4)	No
Surgery (feminizing or masculinizing)	M	M	M	F	M	M	F	M
Gender identity	Male	Male	Male	Female	Male	Male	Female	Male
Gender role	Male	Male	Male	Female	Male	Male	Female	Male
Sexual orientation	Homo-sexual	Homo-sexual	Homo-sexual	Hetero-sexual			Hetero-sexual	
Sexual intercourse	Yes	Yes	No		No	No	Yes	
Masturbation	Yes	Yes	Yes		Yes	Yes	Yes	
Work	Computer technician	General Service–Pharmacy						
Marriage	No	No		No	No	No	Yes	
Children reported	No	No	No	No	No	No	Yes (1)	No
Mental health				Adjusting well				
Parental support of gender assignment				Yes	Yes	Yes	Yes	
Reported height (cm)	163	133	140	138	140	154		
Penile length (cm); (age at time of measurement in years)	4 (1.67)	6 (12)	5 (5)	7 (16)	7 14)	9 (10)		

Table 1. Continued

Reference & country	Jones (42) (2004) USA	Khattab et al. (24) (2017)		Kiviat and Leonard (47) (1978) USA	Lee et al. (5) (2010) USA *(Continued)*			
		Case 1 Pakistan	Case 2 Brazil		Case 1	Case 2	Case 3	Case 4
Prader score	IV*	IV	IV	IV*	IV*	V*	IV*	V*
CAH diagnosis		SV CYP21A 2; Homozygous In2/In2	SV CYP321A 2; Compound heterozygote Ex1 In2 Ex3/ In2	21-OH	21-OH	21-OH	21-OH	21-OH
Delay (years) 46,XX diagnosis	11	3	1.5-2***		3	3-12***	4	4
Age informed of diagnosis (years)	31							
Current age reported years)	31	28	27	17	35	36	45	45
Gender change? (age in years)	No	No	No	No	No	No	No	No
Surgery (feminizing or masculinizing)	M	M	M	M	M	M	M	M
Gender identity	Male	Male	Male	Male	Male	Male	Male	Male
Gender role	Male	Male	Male		Male	Male	Male	Male
Sexual orientation	Hetero-sexual	Hetero-sexual	Hetero-sexual		Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual
Sexual intercourse	Yes	Yes	Yes		Yes	Yes	Yes	Yes
Masturbation	Yes	Yes	Yes		Yes	Yes	Yes	Yes
Work	Proprietor gas station	Soccer player			Business	Executive	Laborer	Welder
Marriage	No (attempted)	Yes	No		No	Yes	Yes	Yes
Children reported	No	No	No		No	No	No	No
Mental health	Suicide	Satisfied			Good		Good	Good
Parental support of gender assignment	Yes	Yes	Yes		Yes			Yes
Reported height (cm)		151	160	142	162	167.5	150.5	150
Penile length (cm); (age at time of measurement in years)		8 (28)	12 (27)	10 (17)				

Table 1. Continued

Reference & country	Lee et al. (5) (2010) USA *(Continued)*							
	Case 5	**Case 6**	**Case 7**	**Case 8**	**Case 9**	**Case 10**	**Case 11**	**Case 12**
Prader score	IV*	IV*	IV*	IV*	V*	V*	IV*	IV*
CAH diagnosis	21-OH	21-OH	21-OH	21-OH	21-OH	21-OH	21-OH	21-OH
Delay (years) 46,XX diagnosis	3-12***	12	3	3-12***	3	3-12***		
Age informed of diagnosis (years)								
Current age reported (years)	47	49	49	53	57	69	35	49
Gender change? (age in years)****	No	No	M-F-M	No	No	No	M-F-M	
Surgery (feminizing or masculinizing)	M	M	M	M	M	M		
Gender identity	Male	Male	Male	Male	Male	Male	Male	Male
Gender role	Male	Male	Male	Male	Male	Male	Male	Male
Sexual orientation	Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual	Hetero-sexual
Sexual intercourse	Yes	Yes	Yes	Yes	Yes			
Masturbation	Yes	Yes	Yes	Yes	Yes		Yes	
Work	Computer programmer	Welder	Disabled	No	Insurance Salesman	Priest	Artist	Laborer
Marriage	Yes	Yes	Yes	Yes	Yes			
Children reported	No	No	No	No	No	No		
Mental health		Good	Poor	Poor	Poor adjustment			
Parental support of gender assignment		Yes	No		Yes			
Reported height (cm)	155	150	163	160	152	160	155	155
Penile length (cm); (age at time of measurement in years)								

Table 1. Continued

Reference & country	Madsen (21) (1963) Germany		Maxted et al. (25) (1965) USA	Money and Daléry (15) (1976) USA			Money (22) (1991) USA	Peris (23) (1960) USA
	Case 1	Case 2		Case 1	Case 2	Case 3		
Prader score	V*	V*	V*	V*	V*	V*	IV*	V*
CAH diagnosis								
Delay (years) 46,XX diagnosis	35		21	12.17	1 month	7.42	< 1 month	18
Age informed of diagnosis (years)	35			Partially informed	Partially informed	Partially informed	18	Never
Current age reported (years)	35		21	18.17	24.25	26.5	24	18
Gender change? (age in years)****	Yes (35)	No	No	No	No	No	M-F-M	No
Surgery (feminizing or masculinizing)	No	No		M	M	M	M	M
Gender identity	Female	Male	Male	Male	Male	Male	Male	Male
Gender role	Male	Male		Male	Male	Male	Male	Male
Sexual orientation	Hetero-sexual	Hetero-sexual		Hetero-sexual	Hetero-sexual	Hetero-sexual		Hetero-sexual
Sexual intercourse		Yes		Yes	Yes	Yes	No	Yes
Masturbation		Yes		Yes, slightly dissatisfied	Yes	Yes		Yes
Work	Army, Monastery			Farm supply business	Construction	Factory, manual work		
Marriage		Yes	Yes		Yes	Yes	No	
Children reported	No	No			No		No	No
Mental health		Fair					Better after surgery	Satisfactory
Parental support of gender assignment				Yes			Yes	
Reported height (cm)	152	152		152	160	152		160
Penile length (cm); (age at time of measurement in years)			5 (21)	5x2 (13)	6x2.5 (19.5)	6.5x2.5 (5.5)		3.5x1.5 (18)

Table 1. Continued

Reference & country	Razzaghy-Azar et al. (17) (2017) Iran		Rosler and Leiberman (26) (1984) Israel *(Continued)*					
	Case 1	Case 2	Case 1 Morocco	Case 2 Morocco	Case 3 Morocco	Case 4 Morocco	Case 5 Morocco	Case 6 Tunisia
Prader score	V	IV	V*	V*	V*	V*	V*	V*
CAH diagnosis	11-beta OHD	11-beta OHD	11-beta OHD	11-beta OHD	11-beta OHD	11-beta OHD	11-beta OHD	11-beta OHD
Delay (years) 46,XX diagnosis	Birth	6	1.8	1.9	1	1.9	5.6	1
Age informed of diagnosis (years)		6						
Current age reported (years)	34	36	20	26	24	21	17	25
Gender change? (age in years)	Yes (12)	No	No	No	No	No	No	No
Surgery (feminizing or masculinizing)	F	M	M	M	M	M	M	M
Gender identity	Female	Male	Male	Male	Male	Male	Male	Male
Gender role	Female	Male						
Sexual orientation	Hetero-sexual							
Sexual intercourse	Yes							
Masturbation	Yes							
Work		Unemployed						
Marriage	Yes							
Children reported	Yes (2)	No						
Mental health	Satisfied	Depressed, expresses regret						
Parental support of gender assignment	Yes	Yes						
Reported height (cm)		147	143-157	143-157	143- 157	143-157	143-157	143-157
Penile length (cm); (age at time of measurement in years)								

Table 1. Continued

Reference & country	Rosler and Leiberman (26) (1984) Israel		Sharma and Gupta (18) (2012) India					
	Case 7 Morocco	Case 8 Turkey	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Prader score	V*	V*	IV*	IV*	IV*	IV*	IV*	V*
CAH diagnosis	11-beta OHD	11-beta OHD	21-OH	21-OH	21-OH	21-OH	21-OH	21-OH
Delay (years) 46,XX diagnosis	2	28	13	15	13	14	14.5	21
Age informed of diagnosis (years)								
Current age reported (years)	23	33	29.1	26.3	23.5	20	18.8	30
Gender change? (age in years)	No	No	No	No	No	Yes (N/A)	No	No
Surgery (feminizing or masculinizing)	M	M	M	M	M	M	M	M
Gender identity	Male	Male	Male	Male	Male	Bigender	Male	Male
Gender role								
Sexual orientation								
Sexual intercourse								
Masturbation								
Work								
Marriage								
Children reported								
Mental health			Good	Good	Good	Poor social adjustment	Good	Good
Parental support of gender assignment			Yes	Yes	Yes		Yes	Yes
Reported height (cm)	143-157	143-157						
Penile length (cm); (age at time of measurement in years)								

Table 1. Continued

Reference & country	Wesselius (2017) Netherlands	Wolfe-Christensen et al. (57) (2002) Germany			
		Case 1	Case 2	Case 3	Case 4
Prader score	V**	V*	V*	V*	V*
CAH diagnosis	21-OH	2-OH, SW	21-OH, SW	11-beta OHD	21-OH
Delay (years) 46,XX diagnosis	12	2.17	0.08		
Age informed of diagnosis (years)					
Current age reported (years)	64	36	31	49	33
Gender change? (age in years)	No	No	No	No	No
Surgery (feminizing or masculinizing)	M	M	M	M	M
Gender identity	Male	Male	Male	Male	Male
Gender role		Male	Male	Male	Male
Sexual orientation					
Sexual intercourse					
Masturbation	Yes				
Work					
Marriage					
Children reported					
Mental health					
Parental support of gender assignment					
Reported height (cm)					
Penile length (cm); (age at time of measurement in years)					

Notes: grey space indicate data not reported.
Surgery marked M indicates masculinizing surgery which may include testicular implants, hysterectomy, and hypospadias repair.
Surgery marked F indicates feminizing surgery such as vaginoplasty.
*Prader score based on description of external genitals.
**Prader score based on no mention of hypospadias.
***Only range given.
****Male-to-female-to-male.
SV: simple virilizing, CAH: Congenital adrenal hyperplasia, N/A: not applicable

The parents reported that their child "…behaved as a female since early childhood… playing with girls, although attending a male school". A pediatric psychiatrist "confirmed a female gender identity and a strong wish to be converted to female. At last report, she was 26 years old, having a "strong desire to marry a man and be a mother" (16, Case 1). The fourth person, at the age of 35 years and being convinced he was a woman, was admitted to hospital, requesting to be changed. He had served in the army in the Second World War but started menstruating at age 26 (21, Case 1). This case died during surgery. Mullerian structures and a hypertrophied right adrenal were found at autopsy, a postmortem diagnosis.

Three individuals initially assigned male had two changes of gender, first to female and then back to male again. One infant was initially assigned male, then two weeks later reassigned to female when CAH was diagnosed, had no surgery and was lost to follow up until age 12 (22). He chose masculinizing surgery. By age 17, he had more friends and appeared happier according to a public health nurse. The remaining two individuals were reported in 2010 (7, Cases 2, 7). The first, age 35, was reassigned in infancy and later self-reassigned as a male after he fought to be reassigned "for 18 years". The second person, age 49, was previously married as a female but eventually self-reassigned to male.

Gender Role/Expression

All male-identified individuals in Table 1 dressed in stereotypical male clothes, had no interest in female toys such as dolls, but in "traditional" male activities. One individual had interests and perspectives that were so "palpably" masculine "that any attempt at reassignment would be disastrous" (23). A subject who was named and reared as a boy, based on the external genitalia, indicated he was content as a minor (16). He proudly behaved and dressed as a male, played with boys and participated in "boys" sports.

Work

These males had typical "male" jobs for the times, including playing soccer (a sole family breadwinner), construction, laborer, pharmacist, businessman, welder, insurance salesman, computer programmer, priest, executive, and computer technician. Only one of four individuals living as women had held a paying job (as a male in the army). Two women were married and mothers. Of the three individuals who changed gender twice, one was an artist, one was a manual laborer, and the third worked as a teacher's aide.

Mental Health

Most cases lacked reports of mental health status. Among the 21 cases that mentioned this, 10 indicated good mental health, 5 satisfactory, and 6 poor. One study (7) included questionnaires with psychometric characteristics. The measures employed were the Rosenberg Self-Esteem Scale, Body Esteem Scale, Masculine Gender Identity Survey, Social Adjustment Self-Report, and Symptom Checklist (SCL-90). Only six of 12 completed these questionnaires. Three who completed them reported that their parents supported them, scored within the average range for self-esteem, body esteem, work, extended family on the SCL-90 global severity index (7, Cases 1, 5, 8). The other three who scored below average on these questionnaires did not have supportive parents (7, Cases 2, 3, 6). A 36-year-old male reported depression and regret (17, Case 2).

Sexual Orientation/Sexual Function

The majority of 46,XX CAH males reported being persistently attracted to and aroused by females and had had vaginal intercourse, with orgasm with women who perceived them as males. Masturbation and non-masturbation sexual fantasies were of females only. Satisfactory sexual function was achieved in all but one case, who reported "slight dissatisfaction" (16). One male had several different girlfriends involving "kissing and petting" beginning at 13 years old (15, Case 3). All six individuals who completed questionnaires reported female sexual partners (7, Cases 1, 3, 4, 6, 8). Sexual function, activity, and satisfaction persisted among those with a male gender rearing. Two males having had sexual intercourse with women completed the International Index of Erectile Function, reporting no problems and one case reported sexual satisfaction including orgasms, which was confirmed by his wife (12, Cases 1, 2, 3).

Marriage/Children

Fifteen males who always lived as males were married to women. Eight (7, Cases 2, 3, 4, 5, 6, 7, 8, 9) had been married between 7 to 34 years with an average duration of 20 years; two (15, Cases 2, 3) without reported duration; one (24, Case 1) for two years; one (21, Case 2) married at age 30; one (11, Case 3) reported in 2002, one (25) reported in 1965 and one (26, Case 7) in 1984.

There were also two individuals who had been gender reassigned twice who either had a serious romantic relationship or had married. One person was initially assigned male then female then reassigned himself to male (7, Case 2). He had a 14-year relationship with a "partner". The second person (7, Case 7) previously married as a female before self-changing to male. There were two individuals initially assigned male but were reassigned to female and had children. One person who changed gender to female at age 12 years eventually married and had two children (17, Case 1). The other person had one child after gender reassignment to female at age four years (19). One wife became pregnant by artificial insemination (26, Case 7) and one wife was beginning artificial insemination procedures (15, Case not identified).

Discussion

Cases of 46,XX CAH having less severe masculinization than those with Prader 4/5 developed a male gender identity and male role expression (8). This shift in behavior has been called Gendered Behavior (27). Research has shown that this "shift" toward male behavior is influenced by androgen exposure, severity of CAH as SW CAH patients generally have significantly more masculinized genitalia and more male gender role/expressions than those without (28,29,30,31), and those with the *CYP21A2* genotype, especially those with the null genotype (3,30). Sexual orientation toward females (27) occurs in 46,XX CAH, with lower sexual attraction to men than controls (32).

Most who established a male gender identity appeared to live successfully in spite of a delayed diagnosis. The diagnosis occurred because of a range of reasons including parents seeking orchidopexy because of the presumption of bilateral cryptorchidism, signs of puberty at a very young age or "hematuria" (menstrual blood) (26). This delay occurred in poor or rural areas and before newborn screening programs were available. Reported cases have been from many countries (Table 1).

A second defining aspect is the male dominant (9) culture in which individuals were born (33,34,35). Examples include a low socioeconomic Pakistani family who urged their financially successful soccer player child to accept male gender assignment (24, Case 1). Some parents preferred a male child, even after an accurate diagnosis and female

gender reassignment was suggested because of possible fertility (17, Case 2, 24, Case 2, 25). Retainment of male gender in India meets socioeconomic needs (18).

Historically, gender assignment for an infant born with DSD was considered a medical emergency, requiring prompt gender assignment, commonly without full disclosure with a warning that birth status should be kept secret from the child. One rural family agreed to female genital normalizing surgery thinking it was emergency therapy (34).

In part, positive psychosexual outcome may have been because parents and professionals were certain regarding maleness and being unaware of the diagnosis. Parental rearing practice studies on gendered behavior are lacking. In one report (36), parents encouraged less girl-typical and more boy-typical toy play in CAH girls. Investigators suggested that the girls' toy preference was influencing their parents' perceptions.

The American Academy of Pediatrics (37) recommends all 46,XX individuals be assigned female with full disclosure and full participation of parents in decision-making for the newborn, but does not address those with delayed diagnosis. The PES Clinical Practice Guidelines (2) state pros and cons of gender assignment and emphasizes that fertility implications must be completely discussed. Surgical decisions must be made with parents and the child, if old enough to provide assent. Experienced consultants are recommended who consider family values, religion and culture. Professionals need to be aware that how information is "framed" impacts on parents' decisions (38,39,40,41) and how and when such knowledge is discovered by patients. One person discovered her diagnosis at the age of 35 years and immediately self-reassigned (21, Case 1). A second, sadly, committed suicide after learning at age 31 years that he was not allowed to marry another genetic female (42).

The best predictor of adult gender identity is initial gender assignment (43) but this is not absolute, since those reported herein changed gender after initially being assigned male at birth. Gender identity may be more fluid than originally thought. We consider it ethically mandatory to inform parents of their option to assign as males if they so choose. Such a position can create controversy within multidisciplinary teams (44) and challenges the PES's Clinical Practice Guidelines (2). These guidelines still take the position that with excellent suppression therapy with glucocorticoids or other medications, such patients can be fertile. However, this has been the perception since the first patients were treated with glucocorticords and this has seldom been demonstrated. Delaying genital surgery is a choice that allows for time to assess gender development with the growing child, providing potential autonomy for the child. Gonadotropin Releasing Hormone analog therapy at or just before pubertal onset can delay puberty allowing more time for monitoring gender development and other domains.

Advantages to temporary assignment as male in infancy without surgery include retaining external genitalia, allowing for later decisions regarding surgery and providing functional anatomy for the child and for sexual function later. While living as a male, he needs to be informed of his diagnosis and its consequences, in an age-appropriate manner, in order to make a fully informed decision at some point in the future. If a male gender develops, feminizing surgery has been avoided while a functional penis is maintained. Negative aspects are increased risk of short adult stature, later surgery to remove female reproductive organs, infertility, cryopreservation, and later hypospadias surgery if necessary and also prostate cancer which was reported in two men (45,46) with one further report (47) of prostatic tissue in a 46,XX male. Testosterone treatment will be needed to induce puberty.

Advantages of female assignment is the potential for normal puberty if adrenal androgens have been well suppressed overtime, which often does not occur sufficiently (2). Feminizing surgery, while challenging and associated with a number of potential problems (48,49), will allow for menstrual flow and intercourse if desired. Feminizing surgery, especially in infants with severe virilization, does not appear to improve nor hamper psychosexual outcome (50). Fertility is possible among the minority with regular menstrual cycles, but studies (51,52,53,54) have documented low frequency of pregnancy, especially those with severely masculinized genitalia at birth and those with SW associated with the null mutation complete 21-hydroxylase deficiency. Anovulation and psychosexual development issues both contribute to infertility (50). Conversely, male genitalia cannot be restored after feminizing surgery should a male gender identity develop or the individual decide to reassign male.

In all of the scenarios, signs of gender dysphoria can appear and should be addressed. Whether assignment is male, female or not assigned, periodic psychological assessments for gender dysphoria are indicated by at least periodic screening. Parents also remain at risk for emotional and other difficulties as the child develops (55,56,57,58). Adolescents and adults can demonstrate problems (59,60). Continued professional support through young adulthood can be helpful (61). In the case of those assigned and being reared male, periodic assessment of gender development is required to determine whether or not genital surgery should

be delayed or recommended in the case of female gender development. The emphasis is upon continuing affirmation of gender identity, realizing that there are multiple variations in gendered behavior. For example, gender identity may be male while sexual orientation may not be typically heterosexual (3,32,43).

The limitations of this report include assessing a small number of retrospective clinical case publications without information from medical records and questionnaires regarding psychometric information, some of which date from 60 years ago. Systematic evaluations are lacking regarding mental health, social life, knowledge of CAH and gender assignment options, general health, drug and alcohol use. Difficulties in achieving compliance among those 46,XX or 46,XY is beyond the scope of this paper.

Conclusion

This study summarizes all outcome data from the global literature on 46,XX CAH whether raised male or female. We believe that the accumulated evidence, though limited, indicates that a 46,XX CAH infant with severely masculinized genitals can successfully establish an adult male gender identity with a reasonable quality of life. Therefore, careful assessment of the person, parents and their cultural beliefs is necessary before reassignment to female is considered. It is highly unlikely that a systematic study, which is needed, comparing overall quality of life outcome of those with severe genital masculinization at birth reared male or female can be accomplished in the foreseeable future. Until then, parents should be fully informed of all options and possible consequences.

Since 1976, the question of whether or not to assign and rear "chromosomal females born with a penis has been an issue of competing values, preserving fertility as a female versus a smoother path through adolescence to adult psychosexual maturity and function as a male" (15). The medical profession still remains divided. We also note that a significant number of CAH patients were not found using neonatal screening testing (62) so it is possible that the Prader 4 and 5 46,XX patients may be missed in countries with screening testing as well as those from rural areas and third world countries.

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Ethics

Authorship Contributions

Concept: Tom Mazur, Peter A. Lee, Design: Tom Mazur, Peter A. Lee, Data Collection or Processing: Jennifer O'Donnell, Peter A. Lee, Analysis or Interpretation: Tom Mazur, Peter A. Lee, Literature Search: Jennifer O'Donnell, Peter A. Lee, Writing: Tom Mazur, Jennifer O'Donnell, Peter A. Lee.

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