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Review

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

Mazur T et al. 46,XX males with Congenital Adrenal Hyperplasia

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ABSTRACT

46, XX individuals born with severely masculinized genitals due to congenital adrenal hyperplasia (CAH) who have been assigned males 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. Reasons are given to support why serious consideration of a male gender assignment and rearing, in certain situations, is justified and should be seriously considered. Disorders of Sex Differentiation (DSD) teams should inform parents of the option of male assignment and rearing in 46, XX CAH infants with severe genital masculinization, 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

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Limited outcome data are available for these patients whether raised male or female. This study summarizes all outcome data from the world's literature and show that careful assessment is necessary before reassignment as female.

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INTRODUCTION

Originally described in 1865 (1) the Congenital Adrenal Hyperplasias (CAH), are autosomal recessive disorders having impaired cortisol synthesis. 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 (SV). CAH occurs in both sexes with external genital masculinization occurring in females. The degree of masculinization is indicated by the Prader Scale (4); the most severe masculinization being four or five. Five indicates a fully formed penis with the meatus at the tip and a fully formed but empty scrotum. Internally reproductive organs are female.

The Pediatric Endocrine Society's (PES) goal 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). 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

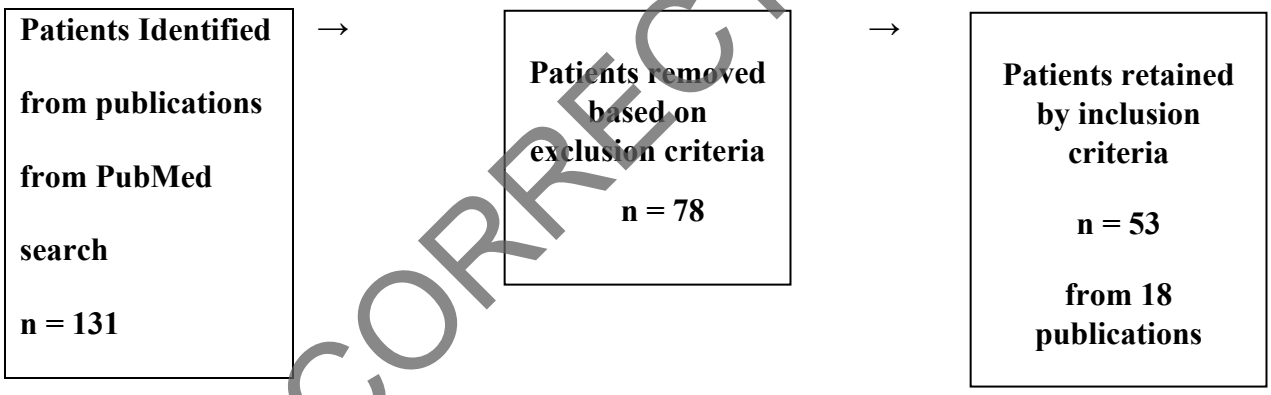
males. The second purpose is to present the pros and cons of full disclosure regarding male gender assignment among severely masculinized infants.

METHODS

A systematic search of PubMed was performed using these key words: 46, XX congenital adrenal hyperplasia, adrenogenital syndrome, assigned male, reared male, Prader stage 4, Prader 5, gender identity, gender role/expression, sexual orientation, sexual function, mental health.

Excluded case reports: [1] children who died in infancy, [2] males who were too young to provide outcome data, [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).

Included were reported cases in English of 46, XX CAH adults, 17 years and older, who were 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.



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

RESULTS

Accurate diagnosis delayed

Delay of the 46, XX CAH diagnosis 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 is 6.8 years although given the

range of years and dates this figure is less meaningful that scanning Table 1. 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) are shown in Figure 1 plotted on a normal distribution population graph (13) based on data from Schoenfeld and Beebe (14). They are also found in Table 1. The median length is 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 percent 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 3 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), 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, he is short (147 cm/4 feet 9 inches), is depressed, expresses regret and cannot find an "appropriate job" (17, Case 2). A case identified as "bigender" 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 and 46, XX karyotype was found and change was recommended because the "tiny" penis precluded a normal male sex life "whereas fertile life in the female sex was clearly possible", and. 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 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 has two biological children and is

"satisfied with her gender" (17, Case 1). The third individual reported at 26 years of age, lived as a male until age 16 years when adrenal hyperplasia was diagnosed. 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 age 26, having a "strong desire to marry a man and be a mother" (16, Case 1). The fourth person, at age 35, being convinced he was a woman, was admitted to the hospital, requesting to be changed. He had served in the Army in second world war but started menstruating.at age 26 (21, Case 1). This person 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. 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 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 soccer (a sole family breadwinner), construction, laborer, pharmacy, businessman, wielder, 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 mention 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 the questionnaires these. 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). A36-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, 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 cases reporting "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 persists among those with a male gender rearing. Two males having had sexual intercourse with women completed the International Index of Erectile Function finding no problems and one case reported sexual satisfaction including orgasms, which was confirmed by his wife (12, Cases 1-3)

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) more in 1984.

There were also two individuals who had been gender reassigned twice who either had a serious romantic relationship or 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 eventually married and has two children (17, Case1). The other person had one child after gender reassignment to female at age four (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 Prade4/5 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 [salt-wasting (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: parents sought 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 urged their financially successful soccer player child to accept male gender assignment (24, Case1). 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 as males in India meets socioeconomic needs (18).

Historically, gender assignment for an infant born with disorders of sexual development (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 without doubts regarding maleness 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 emphasize 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 age 35 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 a 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, that 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 (reported in two men (45, 46). One 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 of 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. Inall 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). Adolescence 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).

LIMITATIONS

Limitations involve a small number retrospective clinical case publications without information from medical records and questionnaires regarding psychometric information. Systematic evaluations are lacking regarding mental health, social life, knowledge of CAH and gender assignment options, general health, drug and alcohol usage. Difficulties in achieving compliance among those 46,XX or 46,XY is beyond the scope of this paper.

Conclusion

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. 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, female can be accomplished in the foreseeable future. Until then, parents should be fully informed of all options and possible consequences.

Since 1976 (15), 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". 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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References

1. Daae E, Feragen KB, Waehre A, Nermoen I, Falhammar H. Sexual Orientation in Individuals With Congenital Adrenal Hyperplasia: A Systematic Review. Front Behav Neurosci. 2020 Mar 13;14:38. doi: 10.3389/fnbeh.2020.00038. PMID: 32231525; PMCID: PMC7082355.

2. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, Meyer-Bahlburg HF, Miller WL, Montori VM, Oberfield SE, Ritzen M, White PC; Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010 Sep;95(9):4133-60. doi: 10.1210/jc.2009-2631. Erratum in: J Clin Endocrinol Metab. 2010 Nov;95(11):5137. Erratum in: J Clin Endocrinol Metab. 2021 Jun 16;106(7):e2853. PMID: 20823466; PMCID: PMC2936060.

3. Frisén L, Nordenström A, Falhammar H, Filipsson H, Holmdahl G, Janson PO, Thorén M, Hagenfeldt K, Möller A, Nordenskjöld A. Gender role behavior, sexuality, and psychosocial adaptation in women

with congenital adrenal hyperplasia due to CYP21A2 deficiency. J Clin Endocrinol Metab. 2009 Sep;94(9):3432-9. doi: 10.1210/jc.2009-0636. Epub 2009 Jun 30. PMID: 19567521.

4. Prader A. Der Genitalbefund beim Pseudohermaphroditismus femininus des kongenitalen adrenogenitalen Syndroms; Morphologie, Häufigkeit, Entwicklung und Vererbung der verschiedenen Genitalformen [Genital findings in the female pseudo-hermaphroditism of the congenital adrenogenital syndrome; morphology, frequency, development and heredity of the different genital forms]. Helv Paediatr Acta. 1954 Jul;9(3):231-48. German. PMID: 13201003.

5. Lee PA, Houk CP, Husmann DA. Should male gender assignment be considered in the markedly virilized patient With 46,XX and congenital adrenal hyperplasia? J Urol. 2010 Oct;184(4 Suppl):1786-92. doi: 10.1016/j.juro.2010.03.116. Epub 2010 Aug 21. PMID: 20728155.

6. Bangalore K, Houk CP, Mohsin F, Lee PA Congenital Adrenal Hyperplasia as a Model to explore Gender Fluidity in Early Life, particularly 46,XX Patients with Male External Genitalia. In: Legato HJ (ed). The Plasticity of Sex: The Molecular Biology and Clinical Features of Genomic Sex, Gender Identity and Sexual Behavior. London: Academic Press, An Imprint of Elsevier 2020; 89-107.

7. Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006 Aug;118(2):e488-500. doi: 10.1542/peds.2006-0738. PMID: 16882788.

8. Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. Arch Sex Behav. 2005 Aug;34(4):389-97. doi: 10.1007/s10508-005-4338-5. PMID: 16010462.
9. Savaş-Erdeve Ş, Aycan Z, Çetinkaya S, Öztürk AP, Baş F, Poyrazoğlu Ş, Darendeliler F, Özsu E, Şıklar Z, Demiral M, Unal E, Özbek MN, Gürbüz F, Yüksel B, Evliyaoğlu O, Akyürek N, Berberoğlu M. Clinical Characteristics of 46,XX Males with Congenital Adrenal Hyperplasia. J Clin Res Pediatr Endocrinol. 2021 Jun 2;13(2):180-186. doi: 10.4274/jcrpe.galenos.2020.2

10. Gillenwater JY, Wyker AW, Birdsong M, Thornton WN. Adrenogenital syndrome producing female pseudohermaphroditism with a phallic urethra. J Urol. 1970 Apr;103(4):500-4. doi: 10.1016/s0022-5347(17)61992-x. PMID: 5437758.

11. Woelfle J, Hoepffner W, Sippell WG, Brämswig JH, Heidemann P, Deiss D, Bökenkamp A, Roth C, Irle U, Wollmann HA, Zachmann M, Kubini K, Albers N. Complete virilization in congenital adrenal hyperplasia: clinical course, medical management and disease-related complications. Clin Endocrinol (Oxf). 2002 Feb;56(2):231-8. doi: 10.1046/j.0300-0664.2001.01463.x. PMID: 11874415.

12. Apóstolos RAC, Canguçu-Campinho AK, Lago R, Costa ACS, Oliveira LMB, Toralles MB, Barroso U Jr. Gender Identity and Sexual Function in 46,XX Patients with Congenital Adrenal Hyperplasia Raised as Males. Arch Sex Behav. 2018 Nov;47(8):2491-2496. doi: 10.1007/s10508-018-1299-z. Epub 2018 Oct 5. PMID: 30291599.

13. Lee PA, Mazur T, Danish R, Amrhein J, Blizzard RM, Money J, Migeon CJ. Micropenis. I. Criteria, etiologies and classification. Johns Hopkins Med J. 1980 Apr;146(4):156-63. PMID: 7366061.

14. Schonfeld WA, Beebe GW. Normal growth and variation in the male genitalia from birth to maturity. J Urol, 1942; 48:759-777. https://doi.org/10.1016/S0022-5347(17)70767-7

15. Money J, Daléry J. Iatrogenic homosexuality: gender identity in seven 46,XX chromosomal females with hyperadrenocortical hermaphroditism born with a penis, three reared as boys, four reared as girls. J Homosex. 1976;1(4):357-71. doi: 10.1300/J082v01n04_01. PMID: 1018100.

16. Bin-Abbas B, Al-Humaida D, Al-Sagheir A, Qasem E, Almohanna M, Alzahrani AS. Divergent gender identity in three siblings with 46XX karyotype and severely virilizing congenital adrenal hyperplasia caused by a novel CYP11B1 mutation. Endocr Pract. 2014 Oct;20(10):e191-7. doi: 10.4158/EP14179.CR. PMID: 25100385.

17. Razzaghy-Azar M, Karimi S, Shirazi E. Gender Identity in Patients with Congenital Adrenal Hyperplasia. Int J Endocrinol Metab. 2017 Jul 30;15(3):e12537. doi: 10.5812/ijem.12537. PMID: 29201068; PMCID: PMC5701969.

18. Sharma S, Gupta DK. Male genitoplasty for 46 XX congenital adrenal hyperplasia patients presenting late and reared as males. Indian J Endocrinol Metab. 2012 Nov;16(6):935-8. doi: 10.4103/2230-8210.102994. PMID: 23226638; PMCID: PMC3510963.020.0216. Epub 2020 Dec 30. PMID: 33374095; PMCID: PMC8186342.

19. Dewhurst J, Gordon RR. Fertility following change of sex: a follow-up. Lancet. 1984 Dec 22;2(8417-8418):1461-2. doi: 10.1016/s0140-6736(84)91646-5. PMID: 6151065.

20. Dewhurst CJ, Gordon RR. Change of Sex. Lancet. 1963 Dec 7;2(7319):1213-6. doi: 10.1016/s0140-6736(63)92939-8. PMID: 14072950.

21. Madsen PO. Familial Female Pseudohermaphroditism with Hypertension and Penile Urethra. J Urol, 1963; 90:466-469. doi:10.1016/S0022-5347(17)64439-2.

22. Money J. Concordance for psychosexual mis-identity and elective mutism: sex reassignment in two cases of 46,XX. In: Money J, Musaph H (eds). Biographies of Gender and Hermaphroditism in Paired Comparisons. New York: Elsevier; 1991; 251-298.

23. Peris LA. Congential adrenal hyperplasia producing female hermaphroditism with phallic urethra. Obstet Gynecol. 1960 Aug;16:156-66. PMID: 14431843.

24. Khattab A, Yau M, Qamar A, Gangishetti P, Barhen A, Al-Malki S, Mistry H, Anthony W, Toralles MB Apóstolos RAC, Canguçu-Campinho AK, Lago R, Costa ACS, Oliveira LMB, Toralles MB, Barroso U Jr. Gender Identity and Sexual Function in 46,XX Patients with Congenital Adrenal Hyperplasia Raised as Males. Arch Sex Behav. 2018 Nov;47(8):2491-2496. doi: 10.1007/s10508-018-1299-z. Epub 2018 Oct 5. PMID: 30291599.

25. Maxted W, Baker R, McCrystal H, Fitzgerald E. Complete masculinization of the external genitalia in congenital adrenocortical hyperplasia. Presentation of two cases. J Urol. 1965 Sep;94(3):266-70. doi: 10.1016/S0022-5347(17)63613-9. PMID: 5828315.

26. Rosler ALE. Enzymatic defects of steroidogenesis, 11 alpha-hydroxylase deficiency congenital adrenal hyperplasia. Pediatr Adol Endocrinol; 1984; 13:47-71.

27. Meyer-Bahlburg HFL. Chapter 10: Psychoendocrinology of congenital adrenal hyperplasia. In: New MI (ed). Genetic Steroid Disorders, 2nd Edition London: Academic Press/Elsevier; 2023;145-158.

28. Long DN, Wisniewski AB, Migeon CJ. Gender role across development in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Pediatr Endocrinol Metab. 2004 Oct;17(10):1367-73. doi: 10.1515/jpem.2004.17.10.1367. PMID: 15526714.
29. Meyer-Bahlburg HF, Dolezal C, Baker SW, Carlson AD, Obeid JS, New MI. Prenatal androgenization affects gender-related behavior but not gender identity in 5-12-year-old girls with congenital adrenal hyperplasia. Arch Sex Behav. 2004 Apr;33(2):97-104. doi: 10.1023/b:aseb.0000014324.25718.51. PMID: 15146142.
30. Nordenström A, Servin A, Bohlin G, et al. Sex-typed toy play behavior correlates with the degree of prenatal androgen exposure assessed by CYP21 genotype in girls with congenital adrenal hyperplasia. J Clin Endocrinol Metab, 2002; 87:5119–5124. doi: 10.1210/jc.2001-011531.

31. Hines M, Golombok S, Rust J, Johnston KJ, Golding J; Avon Longitudinal Study of Parents and Children Study Team. Testosterone during pregnancy and gender role behavior of preschool children: a longitudinal, population study. Child Dev. 2002 Nov-Dec;73(6):1678-87. doi: 10.1111/1467-8624.00498. PMID: 12487486.
32. Zucker KJ, Bradley SJ, Oliver G, Blake J, Fleming S, Hood J. Psychosexual development of women with congenital adrenal hyperplasia. Horm Behav. 1996 Dec;30(4):300-18. doi: 10.1006/hbeh.1996.0038. PMID: 9047259.

33. Hemesath TP, de Paula LCP, Carvalho CG, et al. Controversies on timing of sex assignment and surgery of sex development: A perspective. Frontiers in Pediatrics, 2019; 6:419. doi: 10.3389/fped.2018.00419.

34. Jorge JC, Echeverri C, Medina Y, Acevedo P. Male gender identity in an XX individual with congenital adrenal hyperplasia. J Sex Med. 2008 Jan;5(1):122-31. doi: 10.1111/j.1743-6109.2007.00558.x. Epub 2007 Jul 26. PMID: 17655659.

35. Kuhnle U, Krahl W. The impact of culture on sex assignment and gender development in intersex patients. Perspect Biol Med. 2002 Winter;45(1):85-103. doi: 10.1353/pbm.2002.0011. PMID: 11796934.

36. Wong WI, Pasterski V, Hindmarch PC, et al. Are there parental socialization effects on the sex-typed behavior of individuals with congenital adrenal hyperplasia? Arch Sexual Behavior, 2013; 42:381-391. doi: 10.1007/s10508-012-997-4.

37. American Academy of Pediatrics, Commission on Genetics, Section on Endocrinology, Section on Urology. Evaluation of the newborn with developmental anomalies of the external genitalia. Pediatrics, 2000; 106(1 Pt1):138-142.. doi: 10.1542/peds.106.1.138. PMID: 10878165.

38. Dalke KB, Baratz AB, Greenberg JA. (2002). Protecting children with intersex traits: legal, ethical, and human rights considerations. In: Legato MJ (ed). The Plasticity of Sex: The Molecular Biology and Clinical Features of Genomic Sex, Gender Identity and Sexual Behavior. Cambridge: Elsevier, Academic Press; 109-136.

39. Streuli J, Vayena E, Cavicchia-Balmer Y, et al. Shaping Parents: Impact of Contrasting Professional Counseling on Parents' Decision Making for Children with Disorders of Sex Development. J Sexual Medicine, 2013;10. 10.1111/jsm.12214.

40. Roen K, Hegarty P. Shaping parents, shaping penises: How medical teams frame parents' decision in response to hypospadias. Brit J Health Psychology, 2018. doi: 10.1111.byhp.12333.

41. Timmermans S, Yang A, Gardner M, et al. Does Patient-centered Care Change Genital Surgery Decisions? The Strategic Use of Clinical Uncertainty in Disorders of Sex Development Clinics. J Health Social Behavior, 2018; 59:520535. doi: 10.1177/0022146518802460.

42. Jones HW Jr. The saga of untreated congenital adrenal hyperplasia. J Pediatr Endocrinol Metab, 2004; 17:14811484. doi: 10.1515/jpem.2004.17.11.1481.

43. Meyer-Bahlburg HFL. Treatment guidelines for children with disorders of sex development (Lignes de conduite pour le traitement des enfants ayant des troubles du development du sexe). Neuropsychiatrie de l'enfance et de l'adolescence, 2008; 56: 345-349. doi:10.1016/j.neurenf.2008.06.002

44. Moran ME, Karkazis, K. Developing a multidisciplinary team for disorders of sex development: Planning, implementation, and operation tools for care providers. Advances in Urology, 2012; article ID 604135:1-12. doi: 10.1155/2012/604135.

45. Winters JL, Chapman PH, Powell DE, Banks ER, Allen WR, Wood DP Jr. Female pseudohermaphroditism due to congenital adrenal hyperplasia complicated by adenocarcinoma of the prostate and clear cell carcinoma of the endometrium. Am J Clin Pathol. 1996 Nov;106(5):660-4. doi: 10.1093/ajcp/106.5.660. PMID: 8929478.

46. Wesselius R, Schotman M, Schotman M, et al. A patient (46,XX) with congenital adrenal hyperplasia and prostate cancer: A case report. J Endocr Soc, 2017; 1:1213-1216. doi: 10.1210/js.2017-00281.

47. Kiviat, MD, Leonard JM. True prostatic tissue in 46, XX female with adrenogenital syndrome. Urology, 1978; 12(1):75-8. PMID: 29602. doi:10,1016/0090-4295(78)90375-8.

48. Creighton SM. Adult female outcomes of feminising surgery for ambiguous genitalia. Pediatr Endocrinol Rev. 2004 Dec;2(2):199-202. PMID: 16429106.

49. van de Grift TC, Cohen-Kettenis PT, de Vries ALC, Kreukels BPC, (on behalf of dsd-LIFE). Body image and self-esteem in disorders of sex development: A European multicenter study. Health Psychol. 2018 Apr;37(4):334-343. doi: 10.1037/hea0000600. PMID: 29608076.

50. Callens N, van der Zwan YG, Drop SLS, et al. Do Surgical Interventions Influence Psychosexual and Cosmetic Outcomes in Women with Disorders of Sex Development? International Scholarly Research Network ISRN Endocrinology, 2012; Article ID 276742:8 pages. doi:10.5402/2012/276742.

51. Hagenfeldt K, Janson PO, Holmdahl G, Falhammar H, Filipsson H, Frisén L, Thorén M, Nordenskjöld A. Fertility and pregnancy outcome in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum Reprod. 2008 Jul;23(7):1607-13. doi: 10.1093/humrep/den118. Epub 2008 Apr 16. PMID: 18420648.

52. Slowikowska-Hilczer J, Hirschberg AL, Claaahsen-van der Grinten H, et al. Fertility outcome and information on fertility issues in individuals with different forms of disorders of sex development: Findings from the dsd-LIFE study. Fertility and Sterility, 2017; 108:822-831. doi:

10.1016/j.fertnstert.2017.08.013.

53. Claasssen-van der Grinten HL, Stikkelbroeck NML, Sweep CGJ, et al. Fertility in patients with congenital adrenal hyperplasia. J Pediatr Endocrinol Metab, 2006; 19:677-685.

54. Meyer-Bahlburg HF. What causes low rates of child-bearing in congenital adrenal hyperplasia? J Clin Endocrinol Metab. 1999 Jun;84(6):1844-7. doi: 10.1210/jcem.84.6.5718. PMID: 10372672.
55. Perez MN, Clawson AH, Baudino MN, et al. Distress trajectories for parents of children with DSD: A growth mixture model. J Pediatr Psychol, 2021; 1-11. doi: 10.1093/jpepsy/jsab004.

56. Suorsa KL, Mullins AJ, Tackett AP, et al. Characterizing early psychosocial functioning of parents of children with moderate to severe genital ambiguity due to disorders of sex development. J Urol, 2015; 194:1737-1742. doi: 10.1016/j.juro.2015.06.104.

57. Wolfe-Christensen C, FeldeleD A. Kirk K et al.Degree of genital malformation at birth in children with a Disorder of Sex Development and subsequent Caregive distress. J Urol, 2012; 188:1596-1600. doi: 10.1016/j.juro2012.02.040[1].

58. Hansen-Moore JA, Kapa HM, Litteral JL, Leena Nahata L, Indyk JA,Jayanthi VR, MD, Chan Y-M, Tishelman AC, Crerand CE, PhD Psychosocial Functioning Among Children With and Without Differences of Sex Development *Journal of Pediatric Psychology 2021;*46 (1): 69–79, https://doi.org/10.1093/jpepsy/jsaa089

59. de Vries ALC, Roehle R, Marshall L, Frisén L, van de Grift TC, Kreukels BPC, Bouvattier C, Köhler B, Thyen U, Nordenström A, Rapp M, Cohen-Kettenis PT; dsd-LIFE Group. Mental Health of a Large Group of Adults With Disorders of Sex Development in Six European Countries. Psychosom Med. 2019 Sep;81(7):629-640. doi: 10.1097/PSY.0000000000000718. PMID: 31232913; PMCID: PMC6727927.

60. Jürgensen M, Rapp M, Döhnert U, et al. Assessing the health-related management of people with differences of sex development. Endocrine, 2021; 71:675-680. doi: 10.1007/s12020-021-02627-y.

61. Baratz AB, Sharp MK, Sandberg DE. (2014). Disorders of sex development peer support. In: Hiort O, Ahmed SF (eds). Understanding Differences and Disorders of Sex Development (DSD). Endo Dev. Basel: Karger; 27: 99-112. doi: 10.1159/000363634.

62. Saroufim R, Nebesio TD, Eugster EA. Characteristics of patients with classic congenital adrenal hyperplasia missed on the newborn screen. Horm Res Paediatr. 2023 Nov 22. doi: 10.1159/000535405. Epub ahead of print. PMID: 37992692.

Figure 1

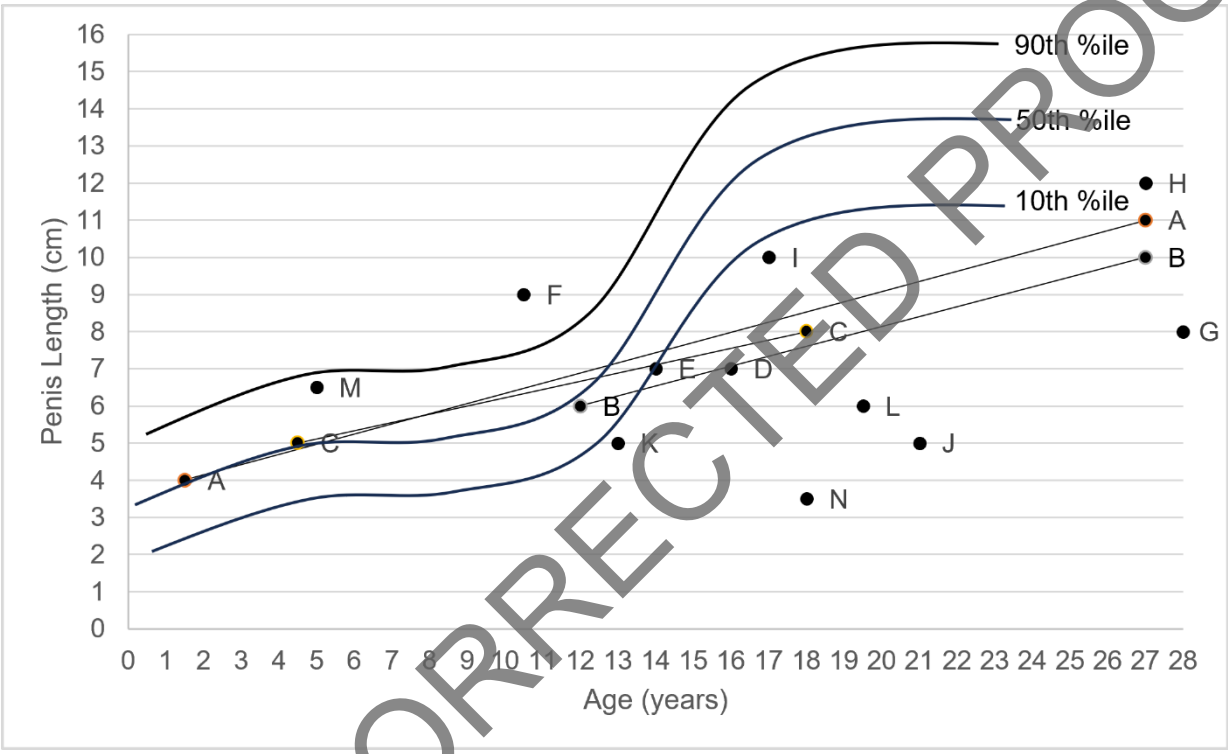

Table 1
CAH 46,XX Adults (≥17) with Severe Virilization Assigned Male

Reference & Country	**Apostolos (2018) Brazil**			**Bin-Abbas (2014) Saudia Arabia**			**Dewhurst (1984) USA**	**Gillenwater (1970) USA**
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3		
Prader Score	IV	V	IV	IV	V	V	V [a]	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)		

Reference & Country	**Jones (2004) USA**	**Khattab (2016)**		**Kiviat (1978) USA**	**Lee (2010) USA** *Continued*			
		Case 1 **Pakistan**	Case 2 **Brazil**		Case 1	Case 2	Case 3	Case 4
Prader Score	IV [a]	IV	IV	IV [a]	IV [a]	V [a]	IV [a]	V [a]
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 [c]		3	3-12 [c]	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)				

Reference & Country	**Lee (2010)** USA *Continued*							
	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12
Prader Score	IV [a]	IV [a]	IV [a]	IV [a]	V [a]	V [a]	IV [a]	IV [a]
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 [c]	12	3	3-12 [c]	3	3-12 [c]		
Age informed of diagnosis (years)								
Current age reported (years)	47	49	49	53	57	69	35	49
Gender change? (age in years)	No	No	No	No	No	No		
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)								

Reference & Country	**Madsen (1963) Germany**		**Maxted (1965) USA**	**Money (1976) USA**			**Money (1991)** USA	**Peris (1960) USA**
	Case 1	Case 2		Case 1	Case 2	Case 3		
Prader Score	V [a]	V [a]	V [a]	V [a]	V [a]	V [a]	IV [a]	V [a]
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	No	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			5 (21)	5x2 (13)	6 x 2.5 (19.5)	6.5 x 2.5 (5.5)		3.5 x 1.5 (18)

time of measurement in years)								

Reference & Country	**Razzaghy Azar (2017) Iran**		**Rosler (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 [a]	V [a]	V [a]	V [a]	V [a]	V [a]
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)								

Reference & Country	**Rosler (1984) Israel**		**Sharma (2012)** India					
	Case 7 Morocco	Case 8 Turkey	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Prader Score	V [a]	V [a]	IV [a]	IV [a]	IV [a]	IV [a]	IV [a]	V [a]
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			Yes	Yes	Yes		Yes	Yes

gender assignment								
Reported Height (cm)	143-157	143-157						
Penile length (Cm); (age at time of measurement in years)								

Reference & Country	**Wesselius (1972) Netherlands**	**Woelfe (2002) Germany**			
		Case 1	Case 2	Case 3	Case 4
Prader Score	V[b]	V[a]	V[a]	V[a]	V[a]
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.

[a]Prader score based on description of external genitals
[b]Prader score based on no mention of hypospadias
[c]Only range given [d]male-to-female-to-male