



Contents lists available at ScienceDirect

## Journal of Pediatric Surgery

journal homepage: [www.elsevier.com/locate/jpsurg](http://www.elsevier.com/locate/jpsurg)

## Review Article

## Gender dysphoria and XX congenital adrenal hyperplasia: how frequent is it? Is male-sex rearing a good idea?

Lisieux Eyer de Jesus<sup>a,b,\*</sup>, Eduardo Corrêa Costa<sup>c</sup>, Samuel Dekermacher<sup>a</sup><sup>a</sup> Pediatric Urology and Surgery Department, Servidores do Estado Federal Hospital, UFF, Rio de Janeiro, Brazil<sup>b</sup> Pediatric Surgery and Urology Department, Antonio Pedro University Hospital, UFF, Rio de Janeiro, Brazil<sup>c</sup> Pediatric Surgery and Urology Department, Porto Alegre Clinics Hospital, UFRS, Porto Alegre, Brazil

## ARTICLE INFO

## Article history:

Received 28 October 2018

Received in revised form 26 January 2019

Accepted 30 January 2019

Available online xxx

## Key words:

DSD

Congenital adrenal hyperplasia

Gender dysphoria

## ABSTRACT

**Introduction:** The frequency of gender dysphoria (GD) among 46,XX congenital adrenal hyperplasia (CAH) patients is unknown. These data are needed to put into perspective the debate about the timing of reconstructive surgery and possible male-raising of the most severely virilized children.

**Objective:** To analyze the frequency of female to male GD between 46,XX individuals raised as females; to identify subgroups with higher chances of showing GD; to describe the results of male-raising among 46,XX CAH patients.

**Materials and methods:** Analytic/descriptive literature review (January 1988 to April 2018).

**Results:** Female-raised patients frequently report the desire to be male, adopt male-typical behavior and are frequently homosexual/bisexual as adults, but this does not correspond to GD. Declared GD among 46,XX CAH patients attained 9% of the reported cohorts, generally in late adolescence/adulthood. We could not prove a relationship between inadequate treatment, null-genotype, late diagnoses, a higher degree of virilization, type of CAH or higher levels of androgens and female to male GD, but this may be due to statistical limitations. Male gender raised patients (MGR) were 10.1% of CAH cohorts included in this review, mostly from under-developed countries, with a high proportion of late diagnoses (76.3%) and familial choices. GD was more common in this group than among female-raised patients. Opting for male gender relates to a short final height, the need for multiple surgeries, surgical castration before puberty and infertility.

**Conclusion:** Both male to female and female to male GD may present in 46,XX CAH patients in a contemporaneous cohort. The proportion of GD is higher among patients raised as males. DSD patients sexual maladjustments are complex and not comparable to the transgender population. Many 46,XX CAH patients with GD define themselves as gender-fluid and do not seek for legal/formal transition. Male-raising Prader 4/5 46,XX CAH patients imply infertility and multiple surgeries. There is no proof that any subgroup of CAH is more prone to GD, despite null genotypes, salt wasting phenotypes and Prader 4/5 cases being related to male-typical behavior and female homosexuality.

**Type of study:** Descriptive/analytic non-systematic REVIEW.

**Level of evidence:** 3

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## Contents

1. Material and methods . . . . .	0
1.1. We made an analytic descriptive, non-systematic literature review . . . . .	0
2. Results . . . . .	0
2.1. Part 1: Gender dysphoria in XX CAH patients (Table 1) . . . . .	0
2.2. Part 2: Male social sex in XX CAH patients (Table 2) . . . . .	0
3. Discussion . . . . .	0
References . . . . .	0

**Abbreviations:** GD, gender dysphoria; MGR, male gender raised; CAH, congenital adrenal hyperplasia; DSD, differences in sexual differentiation; CR, case report; FG, feminizing genitoplasty.

\* Corresponding author at: 52 Presidente Domiciano St, apt 801, Niterói, Rio de Janeiro, Brazil 24210-170. Tel. + 55 21 999859737.

E-mail address: [lisieuxeyerdejesus@gmail.com](mailto:lisieuxeyerdejesus@gmail.com) (L.E. de Jesus).

<https://doi.org/10.1016/j.jpedsurg.2019.01.062>

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Please cite this article as: L.E. de Jesus, E.C. Costa and S. Dekermacher, Gender dysphoria and XX congenital adrenal hyperplasia: how frequent is it? Is male-sex rearing a good idea? Journal of Pediatric Surgery, <https://doi.org/10.1016/j.jpedsurg.2019.01.062>

All guidelines at this point propose that XX CAH patients should be raised as girls, except for late diagnoses in severely virilized patients already being raised as boys. This is justified as these children are capable of natural fertility and pregnancy and by the belief that gender dysphoria (GD) is rare in this group, including in adulthood.

Data concerning GD in CAH patients, however, are scarce, mostly based on case reports or small cohorts and almost always with limited follow up. Pediatric reports most frequently lack data on adults, due to difficulties in long-term follow up and transition of patients from pediatric to adult specialists (gynecologists, endocrinologists and urologists). This is problematic, as GD predominates in late adolescence and adulthood. Clinical specialists lack the expertise to analyze behavioral and sexual problems and mental health specialists may not be aware of clinical and surgical details of the cases: it is challenging to integrate clinical and psychiatric/social data. Multidisciplinary research is not published.

Cultural biases are almost unexplored, but may seriously influence parents' decisions, especially in countries favoring males over females. Illiteracy and unavailability of specialized psychosocial workers and educators may hamper appreciation of the problem by families and health professionals. Religious dogma also interferes with choices.

Contemporaneously some propose to postpone genital reconstruction in DSD patients. Most advocates of this proposal assume specific cultural and sociopolitical understandings about gender issues and/or that the results of feminizing genitoplasties (FG) have less than satisfactory results. The potential consequences of this paradigm change are unknown, as those children and families would have to socially adapt with obviously abnormal genitalia, especially after schooling. Postponing surgery may have consequences over future gender roles and choices, cause maladaptation to a female social role and expose children to bullying and stressful situations. This proposal might be more appropriate for a specific subgroup, but we do not know how to detect patients with a higher probability of GD as adults. The proportion of childhood GD that persists into adulthood and evolves to gender transition has also not been defined.

Parallel to the problems involving the timing and results of FG, some suggest that Prader 5 children should be raised as atypical females or as males (with normal male genitalia) till after puberty/age of consent, but hard data about the results and the possibility of adaptation of highly virilized 46,XX CAH patients as males are not available.

Considering all those questionings, we find it fundamental to review the available data about male social gender and GD in 46,XX CAH patients, if possible characterizing subgroups where GD is more prevalent.

## 1. Material and methods

### 1.1. We made an analytic descriptive, non-systematic literature review

The terms "(congenital adrenal hyperplasia) AND gender", "(XX) AND (congenital adrenal hyperplasia) AND (male gender)" and "(congenital adrenal hyperplasia) AND (gender dysphoria)" were used to find papers thorough PUBMED. The abstracts were then reviewed after eliminating duplications. Papers were then selected to be read *in toto*.

The review extended for 30 years (from January 1988–April 2018). Reviews, editorials and opinion papers were rejected. Due to the specificities of the literature on the theme case reports (CR) were accepted. Gray literature (non-peer reviewed publications, conference papers or lectures) was not included. Papers in English, Portuguese, Spanish and French were accepted.

The review focuses on analyzing gender dysphoria among 46,XX CAH genetic females. We opted to analyze female-raised and male raised separately (sessions 1 and 2 on RESULTS). Our results aimed to define the frequencies of gender dysphoria and social and legal gender transition among those populations, if possible determining the frequency of behavioral and psychiatric-related problems. Statistical

results, whenever possible, were descriptive, considering the limitations of the available data.

## 2. Results

After our initial research, 1770 papers were retrieved; 56 papers were selected to be read *in toto* after review of the abstracts, exclusions and elimination of duplicates. References of the papers were checked in order to find other related papers. After reading of the papers, the analytical review was based on data obtained from 28 articles. Most papers did not detail the methodologies used to diagnose and treat GD, but specialized professionals (psychologists, psychiatrists, sexual therapists) were always involved. Methodological details, whenever available, are cited in the analytical tables.

### 2.1. Part 1: Gender dysphoria in XX CAH patients (Table 1)

Available data about GD in CAH 46,XX patients show severe limitations. Papers limited to small cohorts and case reports with short follow up are the rule, not covering patients' choices after adolescence. Cohorts frequently mix children with adolescents and adults and are difficult to interpret. Cultural specificities may determine serious biases in papers coming from countries with disproportional societal advantages for males and/or religious restrictions, as recognized by various authors.

Some female CAH patients report a desire to be male. This, however, does not correspond to permanent GD and is more frequent among children than adults. In Paterski et al. cohort (43 CAH females, 4–11 yo, 37 salt wasting – SW, 6 simple virilizing – SV), parents declared that their children showed frequent (2/39–5.1%) or occasional (8/39–20.5%) desire to be the other sex [1]. This tendency is corroborated by other authors [2,3]. In research among adult CAH women the patients "identified less" as females when compared to controls and 31% (n = 5) "wished to be males" at least once during the last 12 months, none permanently [3]. Interestingly, Berenbaum et al. compared CAH (n = 43), normal (n = 29) and tomboy (n = 7) girls and demonstrated only 5/43 (11.6%) CAH girls differed significantly from the normal children. Male-type behavior was not related to worse degrees of external virilization. Interestingly, CAH girls showed lesser scores of male-type preferences than "tomboy" biologically normal girls [4]. Male-type play and choice of activities and male roleplaying during childhood correlated with future homosexuality and dissatisfaction with female gender/cross-gendered behavior as adults, but not with GD [3].

Declared GD among 46,XX CAH patients raised as girls varied from 6.3% [5] to 27.2% [6]. Reiner et al. report a 3/9 patients incidence, but his series is severely biased, as patients are part of a cohort of DSD patients being treated for psychiatric problems in a specialized clinic in a country with good acceptance of LGBTQ issues [7]. Khorashan et al. report a lower proportion of GD from a specialized psychiatric clinic in Iran [8].

Most cases manifest in late adolescence/adulthood, in contrast to non-DSD transgenders, that in general exhibit symptoms in late childhood/early adolescence. Only a small minority of children showing a desire to cross-gender or favoring male-typical playing or behavior during childhood show clinical GD as adults. Also, only a small proportion of patients presenting GD do seek formal or legal gender change to the male gender.

We combined 36 cases from 14 papers reporting clear female to male GD attaining 46,XX CAH patients (16/167 from 46,XX CAH cohorts – 9.6% – and 21 CR), mostly adults (27/36, 75%). The papers reviewed originated from India (2), Muslim countries (3), Brazil (1), Europe (2) and USA (6 papers, including one from Porto Rico). In three cases the age of expression of GD was unclear. Three children and 13/27 adults (48.1%) lived as a boy/man.

Some patients showing clear GD have well-adjusted CAH sisters [5,9], suggesting that socio-cultural, familiar and educational issues or availability of medical treatment are not sufficient to explain GD in 46,

**Table 1**

Gender dysphoria among female-raised 46,XX CAH patients (wo: weeks-old, mo: months-old, yo: years-old, Y: yes, N: no; SW: salt-wasting, SV: simple virilizing, NC: non-classic, P: Prader), CR: case report.

Author	Patients age	Evidence of GD	FG	PRADER/HAC TYPE	Transition to male	Details
Gangaher, India, 2016 [17]	6 yo, 22 yo	2/19 (10.5%)	Y/Y	3 SV/ 4 SW	None, ½ clinical depression	22/46 CAH, 19 female gender, 13.5–32 yo (8 SW, 8 SV, 3 NC), psychiatric evaluation + standardized questionnaires
Razzaghy-Azar, Iran, 2014 [5]	27 yo, post-pubertal	2/32 (6.3%)	Y/Y	4, 3	1 transition to male, 1 reverted back to female gender after CAH treatment	32/240 CAH, 48.8% P 4/5, 15 children 17 adults. 1 patient with female well-adjusted CAH sister, psychiatric evaluations and standardized questionnaires.
Silveira, Brazil, 2016 [9]	Adolescent	CR	N (patient refusal)	Unclear, "ambiguous genitalia"	Adolescence, asked for male genitoplasty 62 yo, sexually inactive	Female well-adjusted CAH sister, psychiatric evaluation + psychotherapy
Costa, Portugal, 2016 [11] Reiner, USA, 2005 [7]	5 yo Unclear	CR 3/9 (33.3%)	N Unclear	NC CAH 4/4/5	24 yo 1/3 asked for legal transition.	Psychiatric/psychological methods of evaluation unclear. 9 CAH, XX reared females (selection bias: psychiatric clinic) psychiatric evaluation.
Khorashad, Iran, 2018 [8]	Unclear	2/22 (9.1%)	Y (~3.5 yo)	Unclear	None	22 CAH, > 5 yo (5–23, ~11.5)(selection bias: psychiatric clinic), psychiatric evaluation.
Meyer-Bahlburg, USA, 2006 [2]	Adults	3/63 (4.8%), 5/63 (7.9%) possible GD (verbal expression)	Unclear	All SW, Prader stage unclear	1/3	42 SW, 21 SV, 82 non-classic CAH, 24 controls/ Cohort recruited from 2 specialized clinics by letter, psychiatric evaluations + standardized questionnaires.
Meyer-Bahlburg, USA, 2004 [36]	-	No cases of GD	-	-	-	15 CAH (13 SW, 2 SV), 5–12 yo, psychological testing. No GD, psychiatric evaluation + standardized questionnaires.
Chowdhury, Bangladesh, 2015 [6]	5, 9, 9	3/11 (27.2%)	Unclear	3/4/5	3/11 (22%), ages 5/9/9	11 CAH. 3/11 GD (22%), one 4 yo doubtful gender identity. Girls without GD Prader 1–3 (~2.4), standardized questionnaires.
Kukreti, India, 2014 [12] Lee, USA, 2010 [18]	Late childhood Assigned female as infants, reassigned males as adults, one after marrying man.	CR Cohort of CAH 46 XX living as males	N Y, Y	NC Unclear	17 yo, requested surgery 21 yo 2 cases, regret surgery, strong male libido, 1 suicide attempt.	NC CAH, psychiatric clinical evaluation 12 Prader 4/5, male gender, 35–69 yo, 3 excluded (lack of information, no permission to publish), psychiatric evaluation + standardized questionnaire.
Mayer-Bahlburg, USA, 1996 [13]	Late adolescence/ adulthood	Cohort of 4 46,XX CAH with GD	¾ (2 yo, 2.5 yo, 8 yo)	4/5, SV, SW, SW/ 110Hase deficiency	4/4, 2 surgery and legal transition	28–38 yo. All poor adherence to treatment, ¼ late treatment, all declared females early life (4 mo, 2 wo, 2 neonates). No cross-gender rearing identified. Psychiatric evaluation + standardized questionnaires.
Jorge, Porto Rico, 2008 [37]	11 yo	CR	Y, 11 yo	3, SV	Early 20s, married to woman, seeks legal transition, no masculinizing surgery	Raised as male, crossdressing from childhood, reoriented to female 20 mo. Poor adrenal suppression. Psychiatric evaluation.
Richter-Appelt, Germany, 2005 [33]	Unclear	1/11 CAH (nor-female nor-male identity)	unclear	?, SW	Unclear	Adult cohort DSD + controls, questionnaire. 46,XX CAH sub-cohort (n = 11, 8 SW, 3 SV). Standardized questionnaire.
TOTAL	6 children, 3 unclear, 27 adults or post-pubertal adolescents	36 cases, 21 case reports. GD: 16/167 inside cohorts (9.6%), 5/167 "possible" GD	-	-	3 children, 13 adults.	-

**Table 2**

Results of male-gender raising among 46,XX CAH patients (do: days-old, mo: months-old, yo: years-old, 11OHD: 11 hydroxylase deficiency, SW: salt-wasting, SV: simple virilizing, NC: non-classic, P: Prader), CR: case report.

Author	% MGR	Age of diagnosis/ type of CAH	GD (male to female)	PRADER	Details
Gangaher, India, 2016 [17]	3/22 CAH	18 yo (SV), 3.5 yo (SW), 1 mo (SW)	1 (Prader 3, transition to female 30 yo, previous hysterectomy)	3, 3, 5	22/46 CAH, 13.5-32yo, 8 SW, 8 SV, 3 NC. Psychiatric evaluation + standardized questionnaires
Razzaghy-Azar, Iran, 2014 [5]	3/32 CAH	6/12/6 yo, all 11 OHD	1 Prader 5 12 yo reverted to female (after hysterectomy)	3, 5, 4	32/240 CAH, 48.8% P 4/5, 15 children 17 adults. Psychiatric evaluations and standardized questionnaires.
Sharma, India, 2012 [16]	7/173	6/7 late (7-21 yo, ~14.2)	1/7 "bigender" (FG 3 yo, no treatment for CAH)	1/7 P5	6/7 symptoms (6/7 gynecomastia, 1/7 cyclic hematuria) Gender choice: family needed son (1/7), fear of stigma/Hjras (4/7), ignorance about treatment (2/7). 6/7 well adjusted (hysterectomy, oophorectomy, mastectomy, testosterone). Psychiatric evaluation methods unclear.
Jones USA, 2004 [38]	CR	15 yo, SV	None	4	Death (suicide) 31 yo (could not marry woman as "he was female"). Psychiatric evaluation unclear.
Reiner, USA, 2005 <sup>7</sup>	2/11	Unclear	None	5	DSD cohort, 11 CAH patients. Psychiatric clinical evaluation.
Khattab, Pakistan/Brazil/Porto Rico, 2017 [24]	3 cases (CR)	6 mo-3 yo, 3/3 SV. 3/3 CYP21A2 genotyping.	None	4, 4, 3	2/3 male genitoplasty, 1/3 FG as child (reassigned as male 28 yo, suicidal ideation as adolescent). 3/3 well-adjusted as males, 3/3 married to females. Psychiatric evaluation methods unclear.
Dasgupta, Pakistan, 2003 [39]	CR	3 yo, SV	None	4	Last follow up 13 yo. Psychiatric evaluation methods unclear.
Gupta, India, 2010 [40]	Cohort (n = 7) MGR	Unclear	1/7 "doubtful" male identity	Unclear	7 CAH 46 XX/60 DSD patients raised male, 15-25 yo. Psychiatric evaluation methods unclear.
Kirh, Turkey, 2013 [20]	10 cases, 1 SW, 9 SV	~3.6 yo (5 d-10y)	No comments about GD in follow up. All male identity in first consultation.	4/5	7/10 "cryptorchidism". 1 family refused female gender (5 days-old). Psychiatric clinical evaluation.
Woelffle, Germany/Switzerland, 2002 [22]	10/15 Prader 5	Late, 12 SW, 4 SV	1/7 raised as males	5	3/10 converted to females 7-9 yo (1 well adjusted, 1 "social problems", 1 dysphoric). Psychiatric clinical evaluation.
Lee, USA, 2010 [18]	9 adults 35-69 yo	5/6 late (3-10 yo)	None	4/5	3 excluded (lack of information, no permission to publish). 10 living as males from newborn, 2 presented GD post-FG, converted to males. Regular sexual activity (male, heterosexual), except priest. Psychiatric clinical evaluation + standardized questionnaire.
Sripathi, Saudi Arabia, 1997 [25]	6/51 CAH cases, 2 SW, 1 SV, 2 11OHD (siblings)	4/6 late (3-11 yo), 2 perinatal (siblings), family demanded male gender	None	4/6 P4, 2/6 P5	Follow up 1.5-8 years, one individual 16.5 yo. 3 penoscrotal, 1 distal hypospadias. Psychiatric evaluation methods unclear.
Keir, Scotland, 2009 [19]	CR, 11 OHD	5 yo	Unknown	5	African-Muslim origin. Family refused gender reassignment to female. Psychiatric clinical evaluation.
Al-Maghribi, Jordan, 2007 [21]	7/73	< 6 wo	3/7	Unclear	7 raised as females (diagnosis <8 mo), 1/7 father refused FG (4 yo). 7 stayed as males (follow up 9.5-18 yo), 6/7 OH + masculinizing genitoplasty. Psychiatric evaluation methods unclear.
Bin-Abbas, Saudi Arabia, 2014 [10]	3/4 siblings	Late childhood, adolescence (10 yo, 14yo, 16 yo)	1/3, Prader 4, GD early childhood, social/legal transition to female 17 yo	4, 5, 5	Case report 3 46,XX CAH siblings. Psychiatric clinical evaluation.
TOTALS	38 MGR/377 46,XX CAH (10.1% of cohorts) + 35 case reports	29/38 late, 4/38 < 1 yo and 5/38 unclear	7/38 (18.4%) MGR cohort. (2/38 "doubtful gender", 1/38 bigender)	-	-

XX CAH children. Bin-Abbas et al. describe 3 46,XX CAH siblings born with the same genetic mutation and showing similar androgen levels that developed different gender identities (1 identified as a female and 2 as males) [10].

Inadequate endocrinological control of CAH is a surrogate for long-term exposure to androgens and may influence the expression of GD, as well as late diagnoses. Higher degrees of virilization (Prader 4/5 staging) and/or higher levels of androgens are also suspected to determine a higher probability of GD. Although theoretically logical, these assumptions are not proven in the literature, as seen in Table 1. Moreover, there are reported 2 cases of adult GD in non-classical CAH patients [11,12].

A relationship between the subtype of CAH (SW, SV or non-classic) and GD has not been established. There is a bias determined by the predominance of late diagnosis in underdeveloped countries cohorts. Considering the difficulties to obtain diagnosis and treatment, Prader 4/5 46,XX children with SW CAH frequently die from salt-losing crises in infancy without being diagnosed, selecting SV cases that present later, especially as bilateral cryptorchidism, low height or precocious puberty cases. In other words, late diagnosis and clinical phenotype are not independent variables among communities with limited access to perinatal detection tests for CAH and high levels of perinatal mortality from salt-wasting crises.

One patient with GD reverted to female gender after correct CAH treatment [5] and one male-identified patient developed dubious gender choice after hormonal treatment [13], suggesting that lowering androgen levels may affect cross-gender tendencies in some cases. We were unable to relate cross-gender rearing to future GD.

Some authors relate male-type behavior to genotype. Homozygote Null mutations (including CYP21A3) in females are related to absent enzymatic activity, severe salt-wasting phenotype and genital virilization. In SV forms (related to I172N mutation) approximately 1% of the enzymatic activity is retained. Other forms (non-classical CAH) show genetic mutations that allow better preservation of enzymatic activity. Null mutations may be related to male-type behavior in very recent research [14,15].

Suicide/suicide ideation/psychiatric problems are common among 46,XX CAH patients, but are worse and more frequent among females showing GD [1,8]. The relationship between GD and past FG is unclear, although it seems logical for GD patients to deeply regret previous surgeries and they may develop psychiatric problems secondary to the irreversibility of clitoroplasties and to their previous impossibility to participate on surgical choices. Some cases of psychiatric problems directly related to past FG in GD patients have been reported [16–18].

We could find no data about GD in patients subjected to fetal therapy with dexamethasone, probably due to unavailability of adult patients that were submitted to this treatment.

## 2.2. Part 2: Male social sex in XX CAH patients (Table 2)

Male gender raised (MGR) 46,XX CAH children divide into two main groups:

1. Children with early diagnosis that were raised as males because of non-acceptance of a female gender by the family (in general coming from cultures strongly favoring males on religious, financial or societal grounds) [17,19–21]
2. Late diagnosed children (in general coming from underdeveloped countries without access to early diagnosis and treatment). This last group is diagnosed with late salt-losing crises as infants (most frequently), bilateral cryptorchidism, “precocious puberty” (pubarche), telarche/“gynecomastia” or urethrorrhagia in “normal adolescent males” [19–22].

There are few reports about MGR CAH 46,XX patients, varying in the cohorts reported from 4% [16] to 21.4% [23] (10.1% in a compilation of the cohorts included in this review). Reiner et al. present the higher proportion of 46 XX CAH patients raised as males, but their cohort is

biased, as cases come from a highly specialized mental diseases clinic for DSD patients [7]. Most papers come from underdeveloped countries (10/15 from India/Muslin countries, 5 from USA/European countries and 2 from Brazil and Porto Rico), with a high proportion of late diagnoses (76.3%) and familial choices towards male gender raising due to cultural, societal or economic pressures.

Some authors from Asiatic countries discriminate the reasons for parental male gender choice: males socially favored with more chance of economically maintaining families, fear from stigma/ridicule and stigmatization, ignorance and no access to treatment [16,24,25]. Also, to revert a mistaken previous male assignment is extremely difficult in Islamic societies, even for young babies, as there is a public “naming ceremony” between the 7th and 14th day of life, where the name of the father is eventually changed if the infant is the first male child [23].

GD has been repeatedly reported and may be more common among MGR 46,XX CAH children than among female-raised ones (7/38 MRP among 46,XX CAH cohorts – 18.4%).

Opting for male gender gives rise to three unavoidable problems: (1) final height is usually short for males, (2) need for oophorectomy (for all patients) and hysterectomy (arguably) before puberty, in order to avoid feminization, treatment of “gynecomastia” (female-type breasts) and urethrorrhagia in the patients not previously castrated and (3) infertility as adults [22].

## 3. Discussion

We opted to review the last 30 years, based on the recent modifications of the societal views about gender rights, consequences of FG [26] and new techniques of genital reconstruction [27,28]. The last review about GD related to CAH was published in 2005 [29], and results about male raising were reviewed in 2010 by Lee and Houk [30]. Considering the limitations in the literature, it was not possible to perform a systematic review. This made us opt for an analytic review. Our research confirms the difficulties that were predicted from the beginning of our project. The available data are heterogeneous and important details are frequently missing, especially concerning hormonal treatments, genetic diagnosis, surgical technique and, most of all, psychological and psychiatric methodologies adopted to diagnose GD and behavioral/psychiatric problems. CR and small cohorts predominate. The influence of social and cultural bases is a fundamental determinant of patients and experts choices and, as pointed out in the text and in the tables, cases from specific cultures (especially from Muslin countries and from India) represent a significant part of the data. Also, patients coming from underdeveloped countries (a significant part of our collective cohort) are prone to late diagnosis and non-accessibility to the correct treatment. However, after acknowledging the limitations of this kind of research, we think that the data provided herein are useful to provide a contemporaneous panorama of the available information about the problem.

Until recently the protocols adopted by most experts for gender assignment of DSD patients originated from the 1950s, when the group headed by John Money at Johns Hopkins (USA) suggested that children are born “gender neutral”. Those authors suggested that adjusted family education, genital reconstruction before the second year of life and psychological support conforming to the chosen gender of rearing would create adults well-adjusted to either gender. Gender should be chosen considering preservation of fertility, psychosocial stability and future sexual life, implying that 46,XX CAH patients would always be raised as women, as well as 46,XY children born with “unrecoverable” phalluses [31].

More recently biological influences (“androgen cerebral imprinting”) have been recognized to also exert a determinant role in the determination of sexual behavior [32], leading to new ideas about treatment of Prader 4/5 CAH cases and phallic inadequacy. Based on this controversy and on publications suggesting that early genital surgery may jeopardize the future sexual life and gender choices, some authors and groups of activists advocate for a postponement of FG to treat CAH patients. A

minority group even suggests that male-raising may be the best option for the most virilized 46,XX CAH children (Prader 4/5), especially in late diagnosis cases [16,18].

Human sexual development is complex. Both social-psychological components (“nurture”) and biological elements (genetic and hormonal determinants, “nature”) influence, but the proportional relevance of each one has not been determined. This influence possibly varies from one individual to the other due to subjective factors, even among children living in the same culture and with the same diagnosis, as the cases of differing sexual orientation between siblings with the same diagnosis suggest.

Core gender identity (sense of self as being male, female or some other choice) is frequently confounded with sexual orientation (erotic interest towards females or males) and gender role/behavior (activities chosen preferably by one sex over another in a particular social context). In other words, homosexuality or cross-gendered gender roles/appearance may be wrongly described as GD (the sense of pertaining to the other gender as an individual), especially in lay publications.

Some DSD individuals define themselves as “gender-fluid”. As an example, a study about gender identity in DSD patients describes an adult woman with SW 46,XX CAH as “not identified with female gender” but also “not identified with male gender” as submitted to two different tests to quantify femaleness and maleness [33]. Typical transgendered patients do not usually show uncertainty about gender. Also, male to female transitions are the most common among transgender patients [1], while GD in DSD patients is most frequently from female to male.

It is inappropriate to compare transgendered people to DSD patients or to include DSD cases into transgender cohorts. DSD patients frequently experience gender uncertainty or gender confusion that may be attributed to social issues, personal perceptions and feelings related to the diagnosis, to the presence of ambiguous genitalia/genital surgery, to biological not yet well defined aspects (hormonal milieu, genetic diagnosis, gonadal activity) and/or to atypical post-pubertal development. Those uncertainties mostly do not correspond to GD.

It seems logical that GD is more frequent after prolonged and intense exposition to androgens, such as in late diagnoses (more common among SV cases and patients with no access of early treatment in underdeveloped countries), SW phenotypes and null genotypes (presenting higher androgen levels), inadequate adrenal suppression and Prader 4/5 patients. This, however, has not been proved, in part because late diagnoses in underdeveloped countries frequently address non-salt losing CAH patients (SV phenotype) being raised as boys, a selection bias.

The role of late FG is controversial, especially in individuals raised as males and “converted” to females after the first year of life and to Prader 4/5 individuals. Most data about cerebral androgen imprinting are experimental (in animals), observational or indirectly inferred from biochemical measurements obtained from individuals affected with various DSDs as compared to normal children. Some research infers that cerebral androgen influences through social interactions, drawings and play choices during childhood. Behavioral differences have been demonstrated when comparing CAH girls to normal boys and girls [34], but gender behavior does not correspond to gender identity.

Important questions remain unanswered: are the problems verified in patients secondary to cerebral androgen imprinting or postnatal influences, including familial and societal attitudes towards sexuality? Does cerebral imprinting continue after birth, especially during mini-puberty? If so, for how much time and in which proportion, as compared for fetal life? In other words, is there a sensitive period for the sexual differentiation of the human brain? Does late diagnosis (implying longer exposure to high levels of androgens) influence the final expression of sexuality in 46,XX patients? Does the level of circulating androgens determine the degree of “cerebral virilization”? Do the difficulties with adjusting to repetitive genital surgery/medical manipulations or simply to genital differences influence the sexual development/adjustment of those patients? Are anatomical adjustments added to familiar directional education (“nurture”) enough to

determine the gender of the individual? Does the absence of anatomical reconstruction impair the adjustment of the individual patient/family? What is the proportional importance of the various factors involved?

Those questions have practical implications. Their answers may prove that certain circumstances (late diagnoses, SW forms of CAH, specific genotypes) are biological determinants of gender identity in 46,XX patients. If so, certain subgroups might be preferentially raised as boys/men. However, this research evidenced that Prader 4/5 raised as boys/men from infancy may show GD (male to female) as adults, even in male-favoring cultures. Problems with small penises [35], the need of multiple aggressive surgeries (oophorectomy, hysterectomy, hypospadias reconstruction and insertion of testicular prostheses), infertility and short height as adults lead us to see male-raising as an arguable solution, despite being successful in individual cases. Fine-tuned hormonal treatment, including selective growth hormone usage may help patients attain better heights as adults, but even with the best endocrinological treatment genetic females are shorter than genetic males. To be fair, natural fertility is also disappointing for certain groups raised in the female gender [18], but, of course, in females with ovaries and a uterus chance of pregnancy, either spontaneous or assisted, is much better.

GD is said to affect *circa* 5.2% of 46,XX CAH individuals. Approximately 1/3 of them (<2%) opt to live as males, generally after adolescence [29]. This number, however small, is much higher than the incidence of GD in the standard population (0.005–0.014% among adult natal males and 0.002 to 0.003% among adult natal females in the USA) [1]. Considering both the incidences of CAH and female to male GD in north-American populations, the expected incidence of female to male GD CAH patients would be 1:420 million to 1:1.4 billion, forcing us to recognize that the incidence of female to male GD in this population is higher than expected [13]. This review, based on contemporaneous cohorts, found a similar frequency of female to male GD, with a higher frequency or formal gender transition, but the methodological limitations recommend us to be cautious. It is possible that the evolution of societal acceptance and gender rights have made transition and expression of gender conflicts easier for this population.

Our research suggests that male to female transition between 46, XX CAH patients raised as males is even more frequent than among the female-raised cohort. This was also evidenced by Dressen et al. report (12.1% incidence) [29]. The predominance of CR over cohort studies, the bias towards late diagnosis and specific populations and the relative rarity of the situations are serious problems in the interpretation of these data, however.

Atypical or male-typical behavior (male-type jobs and toys, rough and tumble play, “tomboyish” behavior, stereotypical drawings) and female homosexuality/bisexuality are much more common than GD among 46,XX CAH females [2,34]. Even non-classic CAH patients may show behavioral modifications towards masculinization, as compared to normal controls [2]. Psychiatric problems are also more frequent as compared to typical children or adults, especially anxiety or depressive disorders and drug/alcohol abuse, but it is difficult to infer whether this is secondary to personal gender conflicts/GD, sexual maladjustments, chronic disease and conflicts concerning potential infertility and sexual inadequacy, genital deformities, genital repetitive manipulations or surgeries, social problems, bullying and familiar/social rejection [1,8,35].

To conclude, 46,XX CAH patients may manifest GD when raised either as females or males, but are more frequent among MGR cases. There are serious limitations in the literature that suggest us to interpret those data with caution, but one may assume that male-raising Prader 4/5 46,XX CAH patients is not without risks of future GD. Also, it is not an easy solution, as multiple surgeries are needed and short height as adults are the rule.

DSD patients sexual maladjustments are complex. Many define themselves as gender-fluid “nor female nor male” and most showing GD do not seek legal/formal gender transition. This population is not comparable to transgendered individuals.

There is no proof that any subgroup of CAH is more prone to GD, despite null genotypes, salt wasting phenotypes and Prader 4/5 cases being related to male-typical behavior and female homosexuality.

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