Congenital adrenal Hyperplasia and psychosocial repercussions

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Barbara Caldeira Pires
Medical Student
Institution: Centro Universitário de Belo Horizonte
Address: Rua Machado Nunes, 211, Salgado Filho, Belo Horizonte – MG, CEP: 30550-280
E-mail: barbaraapires1@gmail.com

Isabella Abidalla do Carmo
Medical Student
Institution: Centro Universitário de Belo Horizonte
Address: Rua Líbero Leone, 130, Apt 402, Buritis, Belo Horizonte – MG, CEP: 30493-145
E-mail: isabellaabidalla@gmail.com

Gabriela Guimarães Nogueira
Medical Student
Institution: Centro Universitário de Belo Horizonte
Address: Rua Ouro Preto, 1306, Apt 1302, Santo Agostinho, Belo Horizonte - MG, CEP: 30170-041
E-mail: gabign2007@gmail.com

Rafael Moura de Oliveira
Medical Student
Institution: Faculdade Ciências Médicas de Minas Gerais
Address: Rua José Hemetério Andrade, 357, Buritis, Belo Horizonte - MG, CEP: 30493-180
E-mail: mourarafael98@gmail.com

Joice Ribeiro Lopes
Medical Student
Institution: Centro Universitário de Belo Horizonte
Address: Rua Walter Guimarães Figueiredo, 390, Bloco 1, Apt 503, Buritis, Belo Horizonte - MG, CEP: 30492-030
E-mail: joicerlopes@gmail.com

Luiza Ortolan Passanezi
Medical Student
Institution: Universidade Nove de Julho - Campus Vergueiro
Address: Rua Manoel da Nóbrega, 262, Apto 83, Paraíso, São Paulo - SP
E-mail: luizaortolanpassanezi@gmail.com

Noelly Mayra Silva de Carvalho
Medical Student
Institution: Instituto Metropolitano de Ensino Superior (IMES/Univaço)
Address: Rua Waldir Leite Pena, 145, Silveira, Belo Horizonte - MG, CEP: 31140-420
E-mail: noelly.carvalho@hotmail.com

Luciele Cristofari Torres de Lima
Pediatric Endocrinologist
Institution: Hospital Universitário Dr. Miguel Riet Corrêa Jr. (HU-EBSERH-FURG)
Address: Avenida Flamengo, 515, Casa 3, Ipanema, Porto Alegre - RS, CEP: 91760-120
E-mail: luciele_med@hotmail.com

ABSTRACT

Congenital adrenal hyperplasia (CAH) is a chronic condition, mainly related to lack of the enzyme 21 hydroxylase (21-OH), that belongs to a group of cytochrome P450 enzymes. Individuals with the disorder are exposed to elevated levels of intrauterine androgens as a result of endogenous cortisol deficiency. In the classic form of disease, there is a division between simple virilizaing (VS) and Losing Salt (PS). Prenatal exposure to androgens, especially in individuals with 46 XX karyotype, can influence the mental health of those affected, determining the development of a higher incidence of gender dysphoria (GD), in addition to direct neurodevelopmental, psychiatric and psychosocial disorders. This integrative literature review deals with the main points that associate CAH to DG and other disorders, comparing the existing bibliography for a reflective analysis of the subject. There are few studies available on this topic, and more comparative research is needed for a assertive conclusion.

Keywords: congenital adrenal hyperplasia, gender dysphoria, gender identity, 21 hydroxylase deficiency.

1 INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) refers to a group of enzymatic alterations that affects the adrenal gland. Most frequent subtype is caused by a deficiency of the enzyme 21 hydroxylase (21-OH), whose responsible gene (CYP21A2) is found on chromosome 6p21.2. This enzyme is from the cytochrome P450 group, and it is responsible for converting progesterone into deoxycorticosterone, and 17-hydroxyprogesterone into 11-deoxycortisol (participates in cortisol and aldosterone synthesis, having cholesterol as a precursor). Gene mutation with consequent 21-OH deficiency can lead to a decrease of cortisol and aldosterone plasma concentrations, in addition to an increase of 17-hydroxyprogesterone (17OHP) and androgen hormones concentrations, due to hyperstimulation of hypothalamic-pituitary-adrenal axis1,2. Less common mutations in other genes, such as CYP11A1, HSD3B2, CYP17, CYP11B1 -- whose enzymes also act in the adrenal gland enzymatic cascade --, cause CAH and are responsible for different degrees of external genitals virilization in girls, as well as it occurs in CYP21A2 mutation[3].

Attenuation of cortisol and aldosterone levels, due to 21-OHP deficiency, is one of the main causes of CAH, corresponding to approximately 90% of cases. It is an autosomal recessive disorder with an incidence close to 1:15,000 - 1:10,000 in new borns from Caucasian population, and has been associated with gender issues identified in females[2].

Due to 21-OH deficiency, disease presents in two forms: classical and non-classical. Classical form is divided into Simple Virilazing (VS) and Salt Losing (PS). VS subtype is characterized by multiple degrees of early virilization in females, detected at birth, due to androgen excess. Manifestations range from isolated clitoromegaly to a male-looking external genitalia, with bilateral cryptorchidism. Boys may have normal external genitalia or an enlarged penis and scrotal hyperpigmentation, which are unlikely to be diagnosed at birth[3,4].

When clinical condition is not treated in girls, progressive virilization is observed, with the appearance of pubarche, hirsutism, acne, muscular hypertrophy, delayed menarche, menstrual irregularity, acceleration of growth and loss in final height due to late skeletal maturation[4]. In boys, there is also a deepening of the voice and an increased penis, without an increase in testicular volume.

Among the two subtypes, PS form is the most common, appearing in 75% of cases. It manifests with SV-like alterations associated with a deficiency in mineralocorticoids production. The main one is aldosterone, which acts on renal tubules by increasing sodium reabsorption, associated with potassium and water excretion. When this hormone is in lower concentrations, there is a dysregulation in body's hydro-electrolyte balance. Usually, between five to 15 days of life, dehydration, vomiting, metabolic acidosis, hypovolemic shock and even death can occur, if the treatment is not fast and effective[3,4].

In non-classical form, there is no significant reduction in enzymatic activity. Cortisol deficiency does not occur and the manifestations due to increased plasma androgens appear in late childhood, adolescence or early adulthood. Some of the alterations presented by patients are: precocious pubarche, hirsutism, polycystic ovaries, with oligomenorrhea or amenorrhea, acne and advances in growth and skeletal maturation[4].

Diagnosis of CAH can be performed using the heel prick test, with the aim of detecting the disease early and avoiding complications such as electrolyte imbalance. When there is an alteration in this test, and the occurrence of clinical signs that suggest the pathology, it is important to confirm the diagnosis with serum 17-OHP dosage, genetic tests, adrenal androgen dosage, electrolytes, among other tests[3]. Measurement of plasma renin activity and electrolytes helps to differentiate from classic, salt-wasting or simple virilizing forms. Genetic testing, with identification of bi-allelic pathogenic variants in CYP21A2, confirms the diagnosis of CAH due to 21-OH deficiency and allows more studies. Eectrolyte replacement is essential until the diagnosis of salt-wasting form is ruled out[4,5]. Early diagnostic methods, such as 17-OHP dosage or molecular analysis of the CYP21A2 gene (in amniocytes or chorionic villi), during the eighth week of gestation[3], can be useful to avoid genital ambiguity in females and, also, precocious pseudopuberty in males. It is useful in preventing deaths resulting from the PS form[6,7]

Less common variations of CAH (10% of cases) can present other disorders ,depending on the affected enzyme, such as Systemic Arterial Hypertension (SAH), no development of secondary sexual characters, low levels of androgens, signs of little or absent virilization in boys, hypergonadotrophic hypogonadism, history of maternal virilization during pregnancy and skeletal malformations. Definitive differential diagnosis of these forms, in relation to 21-OH deficiency, are made through specific genetic tests[3].

Treatment varies according to the category of disease presented by the patient. In classical form, glucocorticoids are administered at doses similar to physiological ones, aiming to reduce (partially) androgen secretion by the adrenal, without inhibiting the hypothalamic-pituitary-adrenal axes. Doses should be increased in stressful situations and intense activity. Mineralocorticoids are administered to suppress electrolyte imbalances and normalize renin enzyme[2,4,5]. Patients with PS form need, in addition to cortisol replacement, mineralocorticoid replacement. Infants with PS form also need sodium chloride supplementation (1-2 g,day), usually up to the age of 12 months[2,8,9]. Non-classical form, treatment with glucocorticoids is only indicated if the affected individual presents symptoms[3,8]. Treatment of less incident forms of CAH will depend on the degree of adrenal function involvement and its by-products[3].

Early diagnosis and treatment of CAH are important factors in preventing morbidity and mortality, with the main objective of controlling overproduction of androgens and providing adequate supplementation for adrenal insufficiency. Controlling excess androgens with the need for higher doses of glucocorticoids, associated or not with mineralocorticoids, may increase cardiovascular risk factors. Furthermore, insufficient glucocorticoid therapy can lead to excessive androgens, infertility and the development of adrenal crest tumors, making it a challenge for clinical practice to control the balance in treating these factors[7].

As for the aesthetic aspects, in situations where the external genitalia are altered, surgical intervention is necessary, usually in the first 12 to 18 months of life, in order to reduce psychosocial disturbances and allow a normal sexual life[7]. In some cases, more than one surgical interventions are necessary. It is important to discuss the surgical options for each patient, which may include clitoroplasty, vaginoplasty or urogenital sinus repair, in addition to the risks, benefits and factors likely to be irreversible after the surgical procedure. These patients must be treated at specialized centers by an experienced and multidisciplinary team[6].

CAH can be associated with gender dysphoria, an issue that usually arises in early adolescence, and can be defined as a patient's perCEP:tion of his or her own gender. Consequences generated by this condition occur from the incongruity between gender and genital appearance, which enables social stigmatization, impaired genital self-image, relationship difficulties and several issues that mainly involve the personal identification of these individuals. In most cases, complaints can also be generated

by misinformation about the details of patient condition, which highlights the need to address sexual health and function, as well as fertility and gender identity during this transition process[9]. Several studies also relate the occurrence of CAH to neurodevelopmental disorders, psychiatric disorders and psychosocial development with significant implications in those individuals' quality of life[10,11,12].

Prevalence of GD and psychological disorders associated with CAH is still uncertain, since little research has been carried out on the subject so far, and the researches already made have a small number of participants. This literature review aims to identify the main studies related to the topic and discuss the aspects observed in these patients.

2 METHODS

Integrative literature review, carried out using the following databases: Pubmed, Lilacs and ScienceDirect. Due to problems and differences in indexing processes on these bibliographic databases, we chose to search for free terms, without the use of descriptors. Therefore, a greater number of references were reached, as the topic addressed is poorly studied. Most of the papers published within the pre-established criteria were included. The terms "21 hydroxylase deficiency", "congenital adrenal hyperplasia psychological disorder", "adrenal hyperplasia genders dysphoria", "psychiatric and adrenal hyperplasia" and "congenital adrenal hyperplasia multidisciplinary support" were used for Pubmed search. On Lilacs platform, descriptors "21 hydroxylase deficiency", "adrenal hyperplasia" and "adrenal hyperplasia sexual disorder" were used. On ScienceDirect, descriptor "21 hydroxylase deficiency and gender dysphoria" was used. Original articles published in last 10 years (2010 to 2020) were selected.

After a careful analysis, we select 19 articles, all in English, including cross-sectional descriptive studies, case series reports, case-control studies and cohort studies. Selected works evaluated: association between CAH and gender dysphoria, neurobehavioral disorders, psychosocial and psychiatric disorders. Articles published before 2010 and available only in abstract were excluded.

3 DISCUSSION

Individuals with CAH that have a female chromosomal pattern (46 XX), have gonads compatible with women. However, these patients present excess testosterone produced, when steroidogenic enzymes are deficient, what can lead to the presence of male genitalia. This condition can generate impasses in the attribution of individual's sex, usually defined at birth. Thus, it is common for patients with CAH to request gender reassignment, due to an incorrect initial definition, or dissatisfaction with the pre-established gender, which characterizes GD[9] .

Individuals raised as determined sex constantly report a desire for change, both in terms of appearance and behavior (considering a social determination of sexes). While sex is determined in

nature by biological factors, gender is established by sociocultural influences, which stereotype female and male, associating them to typical behavioral patterns. Recognition of sexes is plastered to a physiological archetype that does not, actually, determine the differentiation between woman and man. In CAH, the occurrence of gender identity disorders is frequent, due to individual's inadequacy to the sex established at birth, which takes into account the genetic factor and,or the appearance of external genitalia[13].

Different studies correlate prenatal exposure to androgens with these changes in the identity of affected individuals, determining a higher incidence of GD, in addition to direct disturbances on neurodevelopment or psychosocial development[6,7,14,15,16]. Mechanism that facilitates the determination of gender has not yet been fully elucidated. It is believed that, added to intrauterine fetal brain masculinization, a similar change occurs due to lack of adherence to glucocorticoid replacement therapy, during childhood and adolescence. In these patients, GD usually manifests itself in early adolescence[6,7].

Although CAH affects both sexes, the increase in the level of androgens is more impactful in individuals with the 46 XX genotype, considering that 46 XY individuals already have comparatively higher levels of these hormones. Therefore, non-compliance with sex determination at birth is more common in 46 XX patients with CAH [17,14].

A study published in "International Journal of Pediatric Endocrinology" shows that, approximately, 5 to 10% of 46 XX individuals with 21-OH deficiency have gender dysphoria, associated with tendencies towards homosexuality, which suggests a higher prevalence in these patients compared to control cases[18]. Other studies also demonstrate that individuals with CAH are more susCEP:tible to psychiatric disorders and DSD[11,17]. Use of research methodologies based on questionnaires and interviews, with a multidisciplinary team, directed exclusively to children with CAH, or them and their parents, resulted in obtaining consistent data[11,18,17].

In 2010, Nermoen *et al.*, through a population-based study in Norway, found that there was a loss in work capacity and health status in individuals with CAH[19]. Confirming this information, in 2018, Khorashad *et al.*, by conducting a study with 71 Iranian patients with gender dysphoria, 22 of whom had CAH, found that individuals with this pathology have disorders in affective areas and considerable anxiety. More than half of studied samples had, at least, one psychiatric condition[12]. Other similar studies reaffirmed the greater tendency towards mental health disorders and lower quality of life in this population[11,20]. It is estimated that girls and women are twice as likely to develop emotional and psychiatric disorders, compared to people without this enzyme deficiency [11].

Evidence suggests that increased activity of hypothalamic-pituitary-adrenal axis, with consequent hypersecretion of corticotropin-releasing hormone (CRH), is associated with the

development of different anxiety disorders, such as: generalized anxiety disorder, major depressive disorder, panic disorder, anorexia, obsessive-compulsive disorder and alcoholism[21,22].

As reported by González and Ludwikowski (2015), patients with PS form, generally, tend to homo-affective tendencies and may manifest discomfort with predefined female gender[23]. These data can be confirmed by a survey carried out in the United Kingdom, with 43 individuals, all females with 21-OH deficiency. It was shown that, compared to control group, there were significant numbers of girls with CAH who declared the desire to belong to another gender, in addition to exhibiting masculin behaviors[24].

People with incipient virilization may, or may not, consent to the predefined female gender. In situations where there is excessive virilization, the affected patients are usually raised as men. There is a difference in categorization, regarding the consent, or not, of sex definition and gender identity. A study carried out in 2018, with 4 patients 46 XX, with severely virilized CAH, and registered as males, indicated association between sex assignment and gender identity. Evaluation through questionnaires and interviews, with a multidisciplinary team, pointed to adequate adaptation of the ones designated as male, with satisfactory sexual activity: erections, libido, orgasms and exclusive sexual attraction for women[25]. However, limitation of this research is the unsatisfactory amount of its sample.

It is important to consider the impact generated by these multiple frames combined between the biological presentation of sex (whether defined by genetic or aesthetic standards) and gender identity itself. A cohort study carried out in 2016, by Gangaher *et al.*, points to the multiple factors involved in genders determination. There were 22 46 XX patients with CAH, of which three were raised as men and 19, as women. Among the 19 female patients, 2 had GD. On the other hand, from individuals who grew up as male, one had GD. Although many of the evaluated patients fit in their pre-determined gender, for those who presented gender dysphoria, other psychiatric disorders were observed, such as anxiety and depressive symptoms[17]. Attribution of gender in CAH is guided by factors related to the degree of genitalia virilization, such as sociocultural and parental influences, in addition to individual's personality.

Differently from what was observed in other studies, an analysis of 34 individuals with 21-OH CAH, showed that only three had gender dysphoria, being considered by the authors to be a rare condition among patients with this disease[26]. A study published in 2012, holding 91 patients with sexual differentiation disorder (40 of them with CAH), showed that 40% experienced suffering related to sexuality and 66% were subject to developing sexual dysfunction, which is related to a negative body image and had began mainly in adolescence. These individuals showed a decline in self-esteem and were often ashamed to expose their genitalia[27].

A multicenter study conducted in Europe found that girls with CAH had similar rates of psychiatric disorders, when compared to individuals with other disorders of sexual differentiation with

a higher depression rates. Symptoms suggestive of autism, assessed by a specific screening protocol (The Short Autism Spectrum Quotient - AQ-10), showed higher rates when compared to those observed in adult population in general (6.7% and 1%, respectively)[10].

A correct approach of this pathology is needed in adolescence, a period in which patients with CAH start to participate more actively in decisions regarding their medical care. These patients may face problems from previous genital surgeries (performed as a child), decisions involving subsequent processes, or even concerns about their genital appearance. Furthermore, adolescents and adults who underwent the surgical procedure during childhood may suffer complications, such as urinary incontinence, clitoris pain, problems related to urination and vaginal stenosis, in addition to difficulties related to sexuality and aesthetic concerns[6].

Attribution of sex is ideally based on preservation of sociability, sexual satisfaction and capacity for procreation, with the relevance of factors analogous to their order of exposure. In individuals with CAH, the establishment of sex should be based on more assertive characters, as behavior and the preference for toys, which correlate with the impression of androgens and future psychosexual orientation, promoting a reduction in the number of corrective genitoplasties in adulthood[18,28].

It is necessary to manage psychosocial issues by trained health givers, since the main goals of treatment in adolescence are to educate the patient about their condition, previous surgeries, treatment possibilities and long-term implications. This approach needs to be appropriate for individuals' age and development, in addition to involving a multidisciplinary team composed of professionals, such as pediatric endocrinologist, pediatric surgeon, pediatric urologist, gynecologist, geneticist, social worker, psychiatrist, among others[6]. Integration of various groups with experience in managing sexual development disorders around the world is essential to help patients on achieving better quality of life.

4 FINAL CONSIDERATIONS

Cosidering controversies involved in attribution of sexes, and the establishment of gender identity, psychosexual orientation is essential in CAH, especially in cases of sexual reassignments. Even if the patient's genitalia converge to a specific sex, the brain of this individual can delineate a personality consistent with the opposite sex. Thus, gender identification can have multiple presentations according to genotype, sexual characteristics and sociocultural influences.

To live with a chronic disease that requires constant care and the need, in some cases. of multiple surgical interventions, partly explain the higher incidence of psychological disorders in these individuals. Positive body image and self-esteem are important for a person's quality of life, including their sexuality and affective relationships as a whole. Early recognition of dissatisfaction signs with the

assigned gender, as well as a reduction in quality of life, enables psychosocial interventions with prevention of psychiatric comorbidity.

Gender identity is a complex issue that involves multiple spheres, in a biopsychosocial aspect. When related to CAH, this discussion becomes even more complex and challenging, which is confirmed by the scarce literature on the subject, that affects the development of definitive conclusions. Therefore, more studies are needed, preferably multicentric, to reach concrete and clarifying conclusions about the topic.

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