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REVIEW ARTICLE

Management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in children and adolescents: review

Abordagem da hiperplasia adrenal congênita pela deficiência da enzima 21-hidroxilase em crianças e adolescentes: revisão

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ABSTRACT

Objective: To describe the diagnosis and clinical management of 21-hydroxylase deficiency (21OH-D), in the current context of including the disease in neonatal screening programs, as well as genetic, pathophysiological characteristics, and manifestations in childhood and adolescence. **Data Source:** Integrative review performed in MEDLINE (PubMed), LILACS (BVS), Scopus, Web of Science databases in the last twenty years, in English and Portuguese; target population: children from early childhood to adolescence; with the use of the terms "neonatal screening"; "congenital adrenal hyperplasia"; "21-hydroxylase deficiency"; "glucocorticoid"; "polymorphisms of the *NR3C1* gene". **Data Synthesis:** Congenital adrenal hyperplasia (CAH) is a group of diseases characterized by enzyme deficiencies in adrenal cortex steroidogenesis. 21OH-D is responsible for 95% of cases and, if not treated early, can lead to death in the neonatal period in its classic form. Neonatal screening for CAH consists of measuring the precursor 17-hydroxyprogesterone (17OHP) in the blood of newborns, allowing rapid diagnostic confirmation and institution of therapy. The implementation of neonatal screening is an advance, but the control of pediatric patients with 21OH-D is complex and must always be individualized. **Conclusion:** The institution of newborn screening programs for CAH has benefits for the prognosis of children with 21OH-D. Its management is multi-professional, individualized and still a challenge even for the specialist. Wide dissemination of knowledge about the disease is desirable to allow better management of these children, especially girls with the disease who have atypical genitalia.

Keywords: Congenital Adrenal Hyperplasia; Neonatal Screening; 21-hydroxylase Deficiency; Glucocorticoid; NR3C1 Gene Polymorphisms.

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RESUMO

Objetivo: Descrever o diagnóstico e manejo clínico da deficiência da 21-hidroxilase (D-21OH), no contexto atual de inclusão da doença nos programas de triagem neonatal, bem como características genéticas, fisiopatológicas e manifestações na infância e adolescência. **Fonte de Dados:** Revisão integrativa realizada nas bases de dados MEDLINE (PubMed), LILACS (BVS), *Scopus*, *Web of Science* nos últimos vinte anos, em língua inglesa e portuguesa; população-alvo: crianças da primeira infância à adolescência; com o uso dos termos "triagem neonatal", "hiperplasia adrenal congênita", "deficiência da 21-hidroxilase", "glucocorticoide" e "polimorfismos do gene *NR3C1*". **Síntese de Dados:** A hiperplasia adrenal congênita (HAC) constitui um grupo de doenças caracterizadas por deficiências enzimáticas na esteroidogênese do córtex adrenal. A D-21OH é responsável por 95% dos casos e, se não tratada precocemente, pode levar ao óbito no período neonatal em sua forma clássica. A triagem neonatal para a HAC consiste na dosagem do precursor 17-hidroxiprogesterona (17OHP) no sangue de recém-nascidos, permitindo rápida confirmação diagnóstica e instituição da terapêutica. A implantação da triagem neonatal constitui um avanço, mas o controle dos pacientes pediátricos com D-21OH é complexo e deve ser sempre individualizado. **Conclusão:** A instituição dos programas de triagem neonatal para HAC tem trazido benefícios para o prognóstico das crianças com D-21OH. Seu manejo é multiprofissional, individualizado e ainda um desafio mesmo para o especialista. Ampla divulgação do conhecimento sobre a doença é desejável para permitir melhor condução dessas crianças, especialmente de meninas com a doença que apresentam genitália atípica.

Palavras-chave: Hiperplasia Adrenal Congênita; Triagem Neonatal; Deficiência da 21-Hidroxilase; Glucocorticoide; Polimorfismos do Gene *NR3C1*.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of disorders characterized by an enzyme deficiency in cortisol biosynthesis. In more than 95% of cases, CAH is caused by a deficiency of the enzyme 21-hydroxylase (21OH-D), which is one of the most common inborn errors of metabolism. It is also the main cause of atypical genitalia without palpable gonads in newborns. The phenotype is dependent on the degree of enzyme deficiency and manifests itself in a continuous spectrum, in different clinical settings and other age groups. Traditionally, disease phenotypes are classified as non-classical (NC), simple virilizing (SV) and salt-wasting (SW) forms, in ascending order of clinical severity. The approach to each of them is different, especially in the pediatric age group.[1-3]

Data Source

An integrative review was performed in Medline (Pubmed), Lilacs (BVS), Scopus, Web of Science databases in the last twenty years, in English and Portuguese; target population: children from early childhood to adolescence; with the use of the terms “neonatal screening”; “congenital adrenal hyperplasia”; “21-hydroxylase deficiency”; “glucocorticoid”; “polymorphisms of the *NR3C1* gene”. The survey resulted in 148 references, of which 53 were selected, with emphasis to more recent papers or published by study groups on congenital adrenal hyperplasia in Brazil.

Data Synthesis

The 21OH belongs to a group of oxidative enzymes (P450) and is responsible for the conversion of

17-hydroxyprogesterone (17OHP) to 11-deoxycortisol and from progesterone to 11-deoxycorticosterone, in the secretion pathways of glucocorticoids and mineralocorticoids, in the adrenal cortex. The replacement of just one of the enzyme's amino acids can produce important losses of its functional integrity, leading to a low catalytic efficiency. In its deficiency, cortisol reduction leads to stimulation of the hypothalamic-pituitary axis, with an increase in adrenocorticotropic hormone (ACTH) through a feedback loop. There is an accumulation of precursors that are substrates for 21-hydroxylation, which are diverted to the androgen synthesis pathway, causing an increase in their production, in addition to the loss of cortisol and aldosterone secretion. (Figure 1) Clinical manifestations in 21OH-D are therefore determined by these three changes.[1-4]

Genetic Basis of 21OH-D

The 21OH-D has an autosomal recessive inheritance and is related to alterations in the human *CYP21A2* gene, mapped to chromosome 6 (6p21.3). Most individuals with the disease are compound heterozygous, that is, they have different variants in the inherited maternal and paternal alleles. The most common genetic mechanisms in D21-OH are microconversion and multi-exon conversion; secondly, the large deletions. *De novo* mutations can also occur but are rarer.[4]

The *CYP21A2* gene is set in a genome region that is highly susceptible to genetic variation. It is a structure made up of genes and pseudogenes between which exchanges of genetic material can occur. DNA sequences are copied from the *CYP21A1P* pseudogene to the active *CYP21A2* gene. Gene microconversion occurs in this way, through the transfer of small DNA sequences, or through the conversion of several protein decoding regions (multi-exon).[5]

During meiosis, uneven crossing-over can lead to deletions and duplications of the entire *CYP21A2* gene and may involve other contiguous genes. Thus, there may be, for example, an association between 21OH-D and Ehlers-Danlos syndrome, related to mutations in the adjacent tenascin gene, *TNXB*. SW-individuals may present with joint hypermobility and a spectrum of other comorbidities associated with connective tissue disorder, including chronic arthralgia, joint subluxations, hernias, and cardiac defects.[6]

Generally, SW subjects have two mutant alleles which block enzymatic activity, while SV tends to carry a severe mutant allele and a moderate one. In contrast, individuals with the NC variant have two mildly compromised alleles. The clinical form in a heterozygous compound individual is defined by the allele with the highest enzymatic activity.

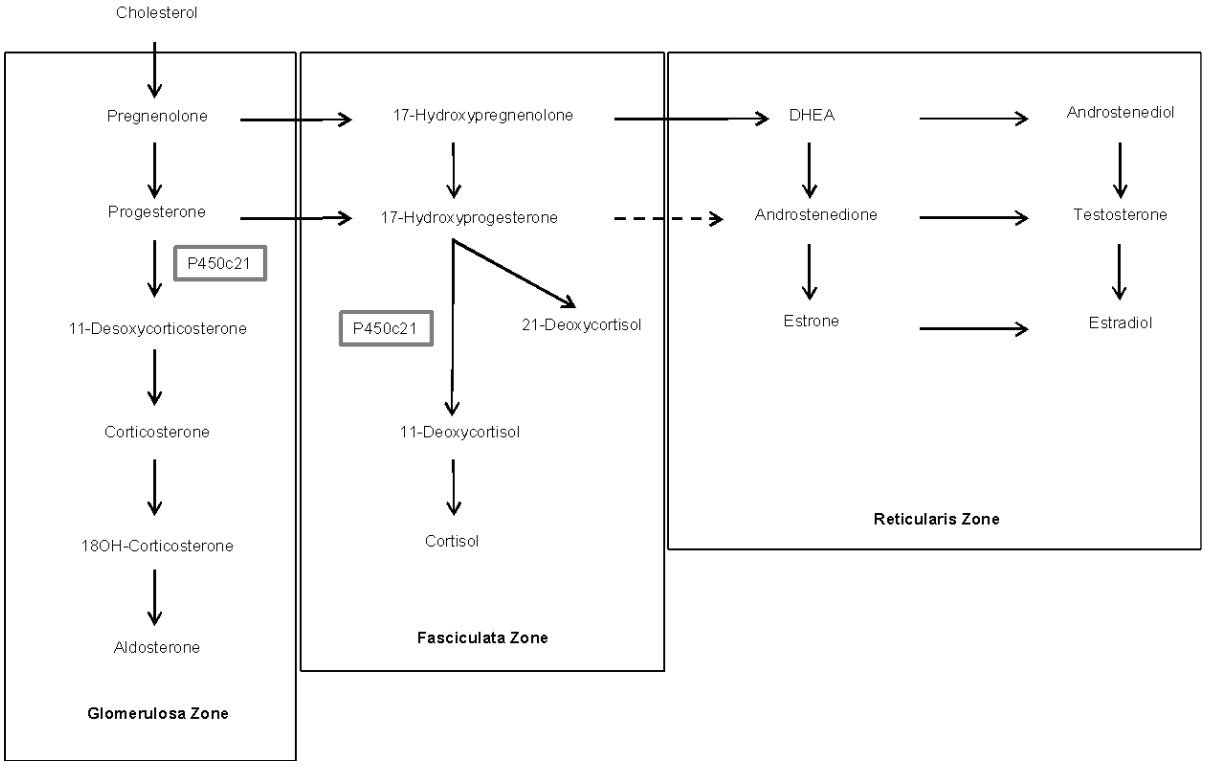

Figure 1. Enzyme blockade in 21-hydroxylase enzyme deficiency.Steroidogenesis in the adrenal cortex occurs in three regions: the outer, glomerulosa zone (mineralocorticoid biosynthesis); fasciculata zone (glucocorticoid biosynthesis); and the more internal, reticularis zone (biosynthesis of sex steroid precursors).[4]
P450c21: 21-hydroxylase enzyme.

Mutations already studied in vitro are grouped into A1 (or Null), A2, B or C, according to 21OH residual activity. Thus, in type A mutations, enzymatic activity is null or minimal (<1%); type B mutations reduce activity to less than 5%; and type C mutations preserve up to 50% of their activity. Overall, there is a good genotype-phenotype correlation.[7,8]

The main mutations were preliminarily studied in Caucasians, whose recombination between the active gene and its pseudogene were responsible for more than 75% of the described pathogenic variants. However, the frequency of pseudogene-independent mutations may be higher, possibly due to the founder effect, usually a result of colonization. In Brazil, as well as in Mexico and Argentina, countries that underwent the predominantly European colonization process, there is a higher prevalence of sporadic mutagenic events with a founding effect.[9-11]

In southern Brazil, the mutations that were most frequently isolated in 21OH-D were: IVS2-13A/C>G, in 55% of alleles among SW-individuals; p.I172N, in 42% of the alleles between SV, and p.V281L, in 70% of the alleles of individuals with the NC form. (Figure 2) In northeastern Brazil, seven microconversions were studied (P30L, I2-Splice, 706_713del8, I172N, V281L, Q318X and R356W), with a predominance of the Q318X mutation.[12-16]

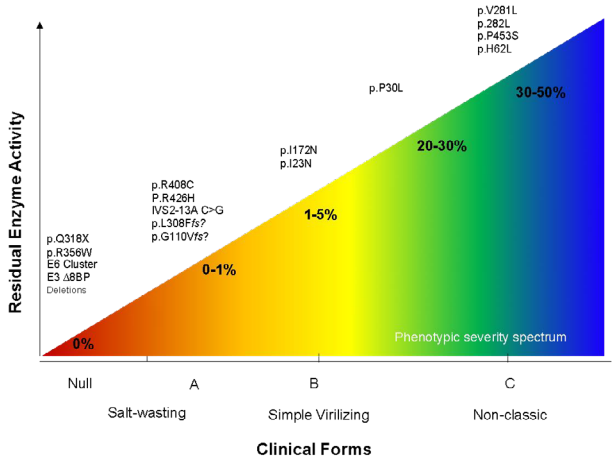

Figure 2. Genotype-phenotype correlation in 21-hydroxylase deficiency; highlighting the most common groups of mutations in Brazil, classified according to the spectrum of clinical presentation[12-16].

Clinical Presentation

The 21OH-D classic form occurs at an overall incidence of 1:15,000 live births[1]. The SW variant is the most severe, accounting for 75% of cases; and SV by about 25%. The SW form is related to early manifestations of mineralocorticoid deficiency. There is excess sodium and insufficient excretion of potassium in the urine, leading to hyperkalemia, hyponatremia, hypovolemia, and hyperreninemia. The newborn may have weak sucking, weight loss, weak crying, lethargy, vomiting and shock in the salt loss crisis and progress to death if left untreated.[3]

Adrenal crisis can occur in the classic form, in situations of stress, leading to severe hypoglycemia, impaired cardiac function and inadequate response to catecholamines, decreased glomerular filtration rate and increased secretion of antidiuretic hormone. Severe cortisol and aldosterone deficiency cause hyponatremic dehydration and shock. Shock is further exacerbated by the deficiency of catecholamines that often occurs in young infants with the SW form.[17,18]

In both SW and SV forms, girls present virilization of the external genitalia due to androgenic excess in the first weeks of intrauterine life, culminating in atypical genitalia at birth, without any involvement of the internal genitalia. They can have different degrees of involvement: from mild clitoromegaly and darkening of the labioscrotal folds, even with a well-defined separation between the urethral and vaginal perineal openings, to the presence of a urogenital sinus after marked androgenization. They often have external genitalia that resemble a perineal hypospadia with *chordee*; the turgid falus is often greater than 0.8 cm in length; and more rarely, it has a typically male appearance, but without palpable gonads.[19]

In clinical practice, the Prader score (1954) is used in the description of atypical genitalia. The degree of external virilization is correlated not only with the severity of the enzyme deficiency, but also with other determinants, such as peripheral sensitivity to androgens. Pelvic ultrasound performed by an experienced examiner provides complementary data to the physical examination about the course of the vaginal and urethral canals or urogenital sinus and confirms the presence of uterus and ovaries as part of the investigation of atypical genitalia. Karyotype should also be studied prior to investigate the disorder of sexual differentiation.[20-22]

The NC form is quite prevalent, with an incidence ranging from 1:1000 to 1:50 in the world population[1]. Most individuals are asymptomatic, but the child with this variant may present precocious pubarche, with or without accelerated growth and bone age. The clinical presentation in female adolescents resembles polycystic ovary syndrome, including hirsutism, acne, and menstrual irregularities or primary or secondary amenorrhea. Among young people with clinical signs of hyperandrogenism, the prevalence of the NC form is 1:10 to 1:25, and it should always be investigated.[23]

Diagnosis

Confirmation of the classic form of 21OH-D, based on clinical suspicion or after neonatal screening (see below), is performed through serum dosage of the adrenal precursor, 17OHP. 17OHP concentrations are elevated and increasing throughout the first month of life in untreated children. 17OHP values ≥10,000 ng/dL (300 nmol/L) are usually found by usual assays (immunoenzymatic), and it is used to confirm the classic form in newborns.[23]

Newborns and young infants with the NC form may have high concentrations of 17OHP, which are occasionally

detected by neonatal screening, but the values decrease in the first months of life. In girls aged 6-15 years with clinical manifestations of the NC variant (precocious pubarche or hyperandrogenism) basal 17OHP concentrations above 200 ng/dL are found. Young women with menstrual irregularities and/or hyperandrogenism have basal higher values, 17OHP ≥540 ng/dL.[24-29]

When the baseline serum 17OHP does not confirm the diagnostic suspicion of the NC form, the challenge test with Cortrosin (0.25 mg ACH, intravenously or intramuscularly) is indicated for 17OHP measurement, after 60 minutes. 17OHP values above 1,000 ng/dL are used for diagnostic confirmation. Influence of different genotypes on stimulated 17OHP values was observed. Overlap of values between heterozygous individuals and normal individuals is also reported. The relationship between stimulated 21-deoxycortisol and cortisol itself can help make this distinction, but this is the main context in which molecular analysis of the gene is useful: it confirms the condition, being important in genetic counseling. Serum elevation of androgens, androstenedione, and testosterone, are also used to confirm the diagnosis.[2,31]

Neonatal Screening for 21OH-D

The main purpose of screening for 21OH-D is the early diagnosis of the classic form, avoiding salt loss signs and symptoms and the incorrect civil registration of girls with genital atypia. In Brazil, screening for 21OH-D was included in the fourth phase of the National Neonatal Screening Program (NNSP), from 2012. The incidence from Brazilian neonatal screening programs is 1:10,000 to 1:14,000 (Goiás, São Paulo, Santa Catarina, Minas Gerais, and Rio Grande do Sul). Most of these states have already accumulated a decade of experience in neonatal screening for 21OH-D.[28-30]

Neonatal screening for CAH consists of measuring 17OHP in the blood of newborns on filter paper, preferably between the third and fifth day of life, and must be followed by rapid diagnostic confirmation for the institution of therapy. Long-term studies in different populations have shown benefits from the implementation of screening: increased number of diagnoses in both sexes, reduction in incorrect records and early deaths.[1]

Despite the notable benefits and wide acceptance of newborn screening for CAH around the world, high false positive rates are a reported problem in most programs. Most of false-positive results are due to variation in 17OHP levels in the neonatal period in newborns submitted to stressful situations in the pre- or neonatal period, or due to prematurity. 17OHP may be falsely elevated because of cross-reactivity with metabolites found in the adrenal under stress, particularly 17-hydroxypregnenolone. However, 17OHP concentrations are also high, due to the immaturity of the adrenal function, with a decrease in the activity of 11-hydroxylase enzymes and, consequently, an increase in the concentration of precursors in relation to the final metabolites of adrenal steroidogenesis. False negatives occur mainly because of early sample collection (before the third day of life) or systemic glucocorticoid use in multiple doses or prolonged use by the mother.[31-33]

Follow-up protocols for children with false-positive results on neonatal screening indicate clinical follow-up and the performance of serial serum tests until normalization for discharge. Cost-benefit assessments are, however, favorable to universal screening for congenital adrenal hyperplasia.[34,35]

Management

The management of 21OH-D classic form is always complex and individualized. In the pediatric age group, the main goals of treatment are to avoid adrenal crisis and allow normal growth and puberty. The NC form requires treatment only in cases where there is precocious pubarche, growth alterations and significant advances in bone age.[1]

The glucocorticoid of choice for pediatric patients is hydrocortisone, which is the pharmaceutical name for cortisol itself. The dose of hydrocortisone acetate recommended in the literature for the treatment of 21OH-D is 10-15 mg/m^2/day. This dose exceeds the physiological level of cortisol secretion in most individuals, which is about 6-9 mg/m^2/day. Slightly supraphysiological doses are needed to adequately suppress adrenal androgen levels, taking care that they are not excessive. The short half-life of hydrocortisone minimizes the growth suppression and other undesirable effects that are often seen with more potent glucocorticoids. With the replacement of doses that allow an adequate balance between the suppression of hyperandrogenism and the prevention of hypercortisolism, most children reach final height within the expected range.[1,36]

When untreated, children with 21OH-D can present with progressive postnatal virilization and evident signs of peripheral precocious puberty in both sexes: enlargement of the phallus in girls and enlargement of the penis without corresponding testicular enlargement in boys, in addition to pubarche, hirsutism, acne, muscle hypertrophy and irreversible deepening of the voice. Children are tall for their age, due to accelerated growth velocity with corresponding advance in bone age, and present final height loss due to early epiphyseal closure. This impairment can be aggravated by the development of gonadotropin-dependent or central precocious puberty (CPP). Due to the lack of treatment or the maintenance of chronically unsatisfactory clinical control, activation of the hypothalamic-pituitary axis may occur, related to chronic hyperandrogenism and bone age advancement, and triggering of central precocious puberty. In these cases, the benefits of pubertal blockage with gonadotropin-releasing hormone analogues should be evaluated, always combined with strategies to improve adherence to hormone replacement therapy.[37]

The prevention of salt loss crises in SW newborns depends on early diagnosis and treatment. In addition to glucocorticoid replacement, these children need mineralocorticoid to maintain fluid and electrolyte

balance. Mineralocorticoid synthesis is controlled by the renin-angiotensin system and by the sodium-potassium-dependent regulatory loop. Angiotensin II and aldosterone are the two most important biologically active products of this system, inducing all the classic actions such as vasoconstriction, sodium retention, tissue remodeling, and pro-inflammatory and pro-fibrotic effects. Renin secretion is stimulated by a range of factors, with renal arterial perfusion being the most important. Mineralocorticoid replacement by fludrocortisone aims to reestablish fluid and electrolyte balance, but without excessive salt retention.[37]

Fludrocortisone is used for mineralocorticoid replacement at a dose of 100–200 µg per day, higher doses (300 µg) may be needed in the initial treatment of newborns with severe salt loss. The use of sodium chloride (1-2 grams/day) is recommended for the first six months of life. Assessment of the patient hydration status, sodium and potassium concentrations and measurement of systemic blood pressure are commonly used to guide mineralocorticoid adjustments in children.[1]

Adrenocortical and adrenomedullary dysfunction in the classic form of 21OH-D can result in severe hyponatremia, hyperkalemia, and hypoglycemia due to impaired production of cortisol and aldosterone secretion, as well as adrenaline. Adrenal crises are potentially serious, especially in young infants, but they can occur at any age and can lead to death in 2-13% of cases. Mortality is associated with insufficient replacement of hydrocortisone (increase in the usual dose) in situations of endocrine-metabolic stress, such as infectious processes, in patients with 21OH-D, incapable of showing an increase in endogenous cortisol secretion.[38]

Due to the risk of hypoglycemia and electrolyte imbalance, family members are instructed to promptly provide oral rehydration serum and foods containing glucose to young children in the event of fever, diarrhea, and vomiting. The usual dose (doubled or tripled) and frequency (every six hours) of hydrocortisone acetate should be increased. If there is intolerance to the oral route, the child should receive in-hospital pediatric support, with parenteral administration of hydrocortisone in increased doses and every six hours. In the emergency room, if there is clinical evidence of shock, the recommended dose is 25 mg for infants, 50 mg for schoolchildren and 100 mg for adolescents. The patient must receive the maintenance dose of glucocorticoid as soon as the condition is stable but must maintain adequate hydration and avoid fasting until the acute event resolves. Other situations that require a stress dose of hydrocortisone: prior to dental surgery with great potential for bleeding or major surgeries, in severe trauma and in the pre-anesthetic for procedures that require sedation (eg, upper digestive endoscopy). Patients must carry an identification card to allow prompt recognition and intervention if necessary.[1,39]

In girls with the classic form, the approach to genital atypia should be widely discussed with the family and surgical intervention decided by consensus. When indicated, genitoplasty, performed by a surgeon experienced in this type of procedure, should be performed as early as possible, after the first year of life.[40]

In adolescence, there is often a worsening in control of patients. Adherence to treatment in pediatric chronic disease in general is related to multiple factors including frequency of medication administration and its side effects; level of understanding and reliability in the proposed therapy and in the health team; level of optimism and support offered by family members; as well as its cultural capital and psychosocial conditions. However, in adolescence, drug non-adherence seems to explain only part of the difficulties in managing patients with 21OH-D. The onset of puberty is associated with changes in hydrocortisone pharmacokinetics. Increased growth hormone and type 1 insulin-like growth factor concentrations lead to decreased 11β-hydroxysteroid dehydrogenase type 1 isoenzyme activity, which reduces cortisone to cortisol in various tissues. Thus, treatment doses in adolescence are often higher than in younger children.[1,40]

Inappropriate treatment in female adolescents can lead to virilization of the genitalia, acne, amenorrhea, and voice changes. On the other hand, male adolescents with persistent ACTH elevation have a 40% risk of presenting intratesticular tumors of adrenal remnants, with impaired spermatogenesis and testosterone production in adulthood. Encouraging the maintenance of correct treatment and early diagnosis of these tumors from the onset of puberty is essential in preventing irreversible testicular damage and infertility.[41,42]

Undertreatment can lead to hyperandrogenism, virilization and progressive advancement in bone age. But hypercortisolism can lead to iatrogenic Cushing, with obesity and bone loss. Both glucocorticoid excess and hyperandrogenism are correlated with an increased risk of short stature in adulthood. Thus, the greatest therapeutic challenge in 21OH-D during adolescence is to ensure adherence, properly controlling the nocturnal increase in ACTH, but without the adverse effects of glucocorticoid treatment.[43]

The monitoring of pediatric patients with CAH must be careful and continuous, ensuring an adequate transition to adult care. Patients should be monitored at a referral service, with periodic consultations in an interdisciplinary approach. Control includes psychosocial, pediatric, endocrinological and, eventually, surgical, and clinical genetic aspects. Special attention must be directed to the emotional aspects of families and children with genital atypia. Endocrinological assessment takes place every three or four months, or more frequently in the first year of life, if necessary; requires a careful physical examination, with assessment of hydration status and blood pressure; in addition to monitoring growth, bone age and pubertal development; and interpretation of exams, which are complementary to clinical aspects.[1-3]

The evaluation of clinical parameters performed together with the levels of androgens that are more stable, as androstenedione, are the key to adequate monitoring. On the other hand, serum 17OHP concentrations persistently within the reference range for the healthy population point

to suppression of the hypothalamic-pituitary axis, due to the excess of administered glucocorticoids, and should be avoided. Monitoring height growth (growth standards) is a sensitive and early indicator of inadequate glucocorticoid replacement before other clinical signs are observed. The acceleration of bone age, monitored annually, is another parameter of therapeutic inadequacy.[1-3]

The treatment of 21OH-D, especially during childhood and adolescence until the closure of the bone epiphyses, is preferably performed with oral hydrocortisone. According to the drug's pharmacokinetics, the dose must be adjusted to the weight and used at least three times a day, at strict times. It is not possible, however, to reproduce the circadian rhythm of cortisol, whose endogenous secretion follows a diurnal pattern, with high and rising plasma levels in the early morning (approximately 5:00-8:00 hours), intermediate levels in the afternoon, levels lows at night. Alternatives to this treatment have been presented, such as the production of slow-release or "dual" hydrocortisone, but there is still a clinical need for a drug that presents a distribution profile closer to the circadian rhythm; and that it makes the proper suppression of ACTH.[44,45]

This is one of the factors that, in addition to the difficulty of adherence and the interindividual variability of response to treatment, can compromise the good control of the disease. The difficulty of controlling 21OH-D is widely recognized and different patterns of clinical response to glucocorticoid therapy are observed, despite an apparent good adherence. It is well established that some individuals are fast glucocorticoid metabolizers. In these, the increase in medication dosage, for example, by twice, does not reflect an expected proportional increase in total cortisol.[46]

The genomic glucocorticoid signaling pathway is mediated by transcription factors activated by the glucocorticoid binding to its intranuclear receptor. In 21OH-D, the study of the functionality of the glucocorticoid receptor does not show differences in relation to the healthy population, neither in terms of the number of receptors nor in terms of binding affinity. Thus, the variability of response to glucocorticoids seems to be, in part, explained by genetic issues.[47-50]

Several factors have been associated with this variability, in different groups of individuals, including the presence of single nucleotide variations, polymorphisms of the *NR3C1* gene, which encodes the glucocorticoid receptor. There are several polymorphisms related to the *NR3C1* gene, the *BclI* and *N363S* variants being associated with increased sensitivity to glucocorticoids. The *ER22*, *23EK*, *GR-9β* variants correlate with clinical measures of decreased sensitivity and better metabolic profile, but increased resistance to glucocorticoids, especially when associated. Further research may lead, in the future, to a more appropriate and individualized treatment of these patients.[50-53]

Conclusions

The management of CAH is multidisciplinary, individualized and still a challenge, even for the specialist. Greater dissemination of knowledge about CAH and its approach allows health professionals to early recognize different phenotypes and appropriately manage, especially, cases of affected girls with atypical genitalia.

Author's Contribution

We describe contributions to the papers using the taxanomy (CRediT): Conceptualization, Investigation, Methodology, Visualization & Writing–review & editing: Cristina Botelho Bara; Ivani Novato Silva. Project administration, Supervision & Writing–original draft: Cristina Botelho Barra; Ivani Novato Silva.

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