CURRENT UPDATE ON THE MANAGEMENT AND TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

ABSTRACT

Congenital Adrenal Hyperplasia (CAH) comprises a set of inherited conditions marked by enzymatic deficiencies within the adrenal steroidogenesis pathway, resulting in compromised cortisol synthesis and, in certain instances, heightened androgen production. Congenital adrenal hyperplasia (CAH) arises from autosomal recessive genetic mutations affecting enzymes crucial for the adrenal glands' biochemical synthesis of glucocorticoids, mineralocorticoids, or sex steroids from cholesterol. The majority of these conditions result in either excessive or deficient production of sex steroids, potentially influencing the development of primary or secondary sex characteristics in affected infants, children, or adults. The management and treatment of CAH are geared towards optimizing hormonal equilibrium, averting adrenal crises, and addressing associated comorbidities. This review presents an updated survey of contemporary approaches to CAH management, encompassing glucocorticoid and mineralocorticoid replacement therapies, along with strategies to alleviate androgen excess. Furthermore, it is required that we look into emerging treatments, including novel pharmaceutical interventions and advancements in genetic and reproductive technologies. The complexities and possibilities inherent in the comprehensive care of individuals with CAH, involving collaboration among endocrinologists, geneticists, and reproductive specialists, are also examined. This review presents an updated survey of contemporary approaches to CAH management, encompassing glucocorticoid and mineralocorticoid replacement therapies, along with strategies to alleviate androgen excess. By scrutinizing recent advancements, this abstract provides valuable insights into the dynamic

landscape of CAH management, emphasizing the imperative for sustained research efforts to augment the well-being of affected individuals.

Keywords: congenital adrenal hyperplasia, CAH, management of CAH, glucocorticoid replacement, mineralocorticoid therapy.

INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a spectrum of disorders, all of which commonly arise due to defects in steroidogenesis, the complex process that is responsible for cortisol production in the zona fasciculata of the adrenal cortex. (1)

This intricate pathway involves five enzyme-mediated steps, and CAH manifests when there is a deficiency in any one of these enzymes. (2)

Within the scope of CAH, a prevalent genetic cause is mutations or deletions of CYP21A, contributing to a 21-hydroxylase deficiency observed in 90% - 95% of cases of adrenal hyperplasia.(3) Additionally, mutations or partial deletions altering CYP21A are not uncommon. The estimated prevalence of CAH stands at one case per 60 individuals in the general population, but this figure surges to one in three within genetically isolated communities featuring a more restricted gene pool.(4)

Distinct populations exhibit varying patterns of CAH. For instance, 21-hydroxylase deficiency, responsible for over 90% of all CAH cases, is prevalent across diverse populations. Conversely, 11-beta-hydroxylase deficiency, another form of CAH, is more frequently identified in individuals of Iranian, Jewish, or Moroccan descent.(5)

The impaired function of enzymes at each stage of adrenal cortisol biosynthesis results in a distinct combination of elevated precursors and deficient end-products, defining the unique clinical manifestations of each CAH subtype.(6) The intricate interplay of genetic factors and

enzymatic disruptions underscores the complexity of CAH and emphasizes the need for tailored approaches to understanding and managing this diverse spectrum of disorders.

TYPES OF CONGENITAL ADRENAL HYPERPLASIA

The impaired cortisol synthesis starts off a cascade of effects characterized by chronic elevations of adrenocorticotropic hormone (ACTH) through the negative feedback system. (7)

This prolonged ACTH stimulation leads to an overstimulation of the adrenal cortex, culminating in hyperplasia - a condition marked by an abnormal increase in the number of cells - and an excessive secretion of the precursors linked to the enzymatic defect.(6)

The diverse forms of congenital adrenal hyperplasia (CAH) consist of a spectrum of genetic mutations affecting the enzymes critical for cortisol production. These mutations result in distinct clinical presentations, each associated with specific challenges and manifestations. (8)

The forms of CAH can be summarized as follows:

Lipoid CAH:

With onset at birth, results from a deficiency in the StAR protein, leading to the absence of sexual development in females. The condition presents with salt wasting, and its genetic basis involves mutations in the StAR gene, resulting in low levels of all steroid products.(9)

3β-HSD deficiency:

This is a congenital condition and is characterized by virilization in females and hypo-virilization in males. Salt wasting occurs, and mutations in the HSD3B2 gene lead to elevated levels of DHEA and 17-pregnenolone, along with low androstenedione, testosterone, and electrolyte imbalances.(10)

17α-OH deficiency:

This is also congenital, involves the P450c17 enzyme, and manifests as hypo-virilization in males with hyperkalemic low-renin hypertension. The genetic basis lies in mutations in the HSD3B2 gene, resulting in elevated levels of DHEA and 17-pregnenolone, along with electrolyte imbalances.(11)

21-OH deficiency (Classic form):

It is characterized by salt wasting and occurs congenitally due to mutations in the P450c21 enzyme. Females exhibit prenatal virilization, while males remain unchanged. The CYP21 gene is involved, leading to elevated 17-OHP, DHEA, and androstenedione, as well as electrolyte imbalances.(12)

21-OH deficiency (Non-classic form):

It is postnatal in onset and leads to hyperandrogenism postnatally with normal genitalia at birth. The CYP21 gene is implicated, causing elevated 17-OHP, DHEA, and androstenedione upon ACTH stimulation.(13)

11β-OH deficiency:

This is a congenital condition, that involves the P450c11B1 enzyme and results in virilization in females and unchanged males. Low-renin hypertension is a characteristic feature, with the CYP11B1 gene being responsible for elevated levels of DOC, 11-deoxycortisol, and androgens, along with electrolyte imbalances.(14)

P450 Oxidoreductase deficiency (POR):

This is a congenital condition, that leads to under-virilization in males and unchanged females with variable mineralocorticoid deficiency. (15)

CURRENT MANAGEMENT AND TREATMENT PROTOCOLS FOR CONGENITAL ADRENAL HYPERPLASIA

The primary objective of therapy in Congenital Adrenal Hyperplasia (CAH) is twofold: to address the deficiency in cortisol secretion and to mitigate the overproduction of adrenocorticotropic hormone (ACTH).

Effective treatment involves the administration of glucocorticoids, which serve to correct cortisol deficiency and simultaneously suppress the excessive production of ACTH.(16)

In normal practices, by employing glucocorticoid therapy, the stimulation of the androgen pathway is reduced, preventing additional virilization. This intervention plays a crucial role in maintaining a hormonal balance, thereby averting further masculinization. (17)

Additionally, appropriate glucocorticoid management facilitates normal growth and development, ensuring that individuals with CAH can attain their full potential without the complications associated with uncontrolled androgen excess. (18)

However, recent data from international and German-Austrian patient registries shed light on prevailing practices. These reports confirm that the predominant approach to CAH treatment involves the use of hydrocortisone, which mimics the physiological glucocorticoid, cortisol. Notably, patients receive median doses of approximately 14 $mg/M^2/d$ throughout much of childhood and adolescence.(19)

It is noteworthy that these doses are considered supraphysiological, given that the physiological cortisol secretion in the absence of CAH is approximately 6-8 $mg/M^2/d$. The utilization of higher-than-normal doses poses an inherent risk of comorbidities. (20)

Recent registry findings indicate that individuals with CAH, compared to the general US population, exhibit a higher prevalence of several health issues during childhood,

including,obesity, fasting hyperglycemia,insulin resistance,hypertension, and reduced levels of high-density lipoprotein (HDL). This trend persists into adulthood, with patients with CAH showing increased rates of obesity, hypertension, and insulin resistance.(21)

The observed health disparities highlight the importance of ongoing research to refine and optimize glucocorticoid replacement regimens for CAH, aiming to strike a balance between therapeutic effectiveness and minimizing the associated risks of comorbidities.(22)

The overarching goal is to enhance the quality of life for those affected by CAH through targeted interventions that address the underlying hormonal imbalances and associated symptoms.

Here is an overview of the current recommendations and followed treatment regimens for congenital adrenal hyperplasia (CAH):

Alternative Hydrocortisone Preparations:

A notable challenge with hydrocortisone, the standard treatment for Congenital Adrenal Hyperplasia (CAH), arises from the limited availability of smaller dosage options in certain locations. (23)

In many instances, the smallest tablets available are 5 or 10 mg, posing difficulties in precise dose titration, particularly for small children. Although alternatives such as custom-compounded suspensions or encapsulated powder exist, not all locales have access to high-quality compounding pharmacies, and concerns about compounding errors have been reported.

Alkindi®:

To address these challenges, a new dosage form has emerged in the form of Alkindi® by Eton Pharmaceuticals. Alkindi® comprises encapsulated micro-tablets or sprinkles, allowing for the opening of capsules and administration of the micro-tablets with a small amount of liquid or other excipients. (24)(25)

This significant cost disparity may present challenges in widespread adoption and accessibility, emphasizing the need for considerations of both efficacy and affordability in the management of CAH.(26)

Chronocort®:

A modified-release preparation known as Chronocort®, developed by Diurnal in the UK, has undergone studies in patients with Congenital Adrenal Hyperplasia (CAH).

This formulation exhibits delayed action, taking effect four hours after intake, and provides sustained cortisol release. Administered at 11 PM, this delayed release mirrors the natural overnight rise and subsequent morning peak of cortisol. A second dose is given at 7 AM, ensuring a consistent cortisol supply throughout the day.(27)

Results from a phase III trial involving 122 patients with classic CAH demonstrated superior hormonal control during the early morning and early afternoon compared to patients receiving standard glucocorticoids. (28)(29)

These findings suggest that, despite not meeting the predefined primary measure, the modified-release preparation demonstrated a notable improvement in the control of morning serum 17OHP levels, offering a potential advantage over standard glucocorticoid therapy in managing Congenital Adrenal Hyperplasia.(30)

These findings suggest that the Chronocort® modified-release preparation may offer improved hormonal control during specific periods of the day compared to conventional glucocorticoid therapy. While the primary endpoint was not achieved, the observed increase in the percentage of patients with controlled morning serum 17OHP highlights the potential of this innovative formulation in optimizing the management of CAH. Further research and clinical experience may provide additional insights into its long-term efficacy and safety.

Abiraterone acetate:

Abiraterone acetate, a potent inhibitor of the enzyme CYP17A1, is primarily employed in the treatment of prostate cancer. In a study involving six adult women, the addition of abiraterone acetate at doses ranging from 100 to 250 mg per day to a background therapy of hydrocortisone (HC) at 20 mg per day normalized androstenedione levels. (31)(32)

In contrast, for patients with non-classic CAH (NC CAH), abiraterone acetate monotherapy might result in DOC accumulation unless combined with glucocorticoid therapy or a mineralocorticoid receptor antagonist.

Additionally, its use in pubertal girls would necessitate concurrent estrogen treatment, such as oral contraceptive pills. Careful consideration of these factors is crucial when contemplating the use of abiraterone acetate in different subpopulations of individuals with CAH. (33)

The inadequacies of current treatment for 21-hydroxylase deficiency (21OHD) are widely acknowledged, leading to the heightened risk of severe long-term complications. Clinicians grapple with the consequences of elevated adrenal androgens in patients who are either untreated or receiving suboptimal treatment.

Simultaneously, they face challenges associated with the effects of cortisol in patients who may be overtreated. Until more advanced interventions, such as gene therapy or adrenocortical cell transplantation, become viable options for restoring regulated adrenal steroid production within the hypothalamic-pituitary-adrenal (HPA) axis, daily glucocorticoid replacement therapy remains an essential component of management.

The primary hurdle in this therapeutic approach lies in effectively suppressing adrenal androgens produced by the chronically stimulated adrenal cortex, reflecting the intricate balance clinicians must strike in addressing the complex hormonal dysregulation characteristic of 21OHD.

CONCLUSION

Ongoing research in the field of Congenital Adrenal Hyperplasia (CAH) encompasses the exploration of alternative dose forms of hydrocortisone, as well as the investigation of adjunctive treatments aimed at reducing androgen levels or adrenocorticotropic hormone (ACTH). Additionally, gene therapy is emerging as a promising avenue for further study in patients with CAH. As these areas of study progress, they contribute to the evolving landscape of CAH research and may pave the way for more tailored and effective therapeutic options for individuals affected by this condition. Continued advancements in understanding the genetic and molecular basis of CAH are instrumental in developing innovative and personalized approaches to enhance patient outcomes.

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