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Congenital Adrenal Hyperplasia: A Review of Current Knowledge and Future Directions

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Abstract:
Introduction: Congenital adrenal hyperplasia (CAH) is a group of diseases in which genetic defects occur that disturb the synthesis of cortisol. The most common variant of CAH (95%-99%) is caused by 21-hydroxylase deficiency as a result of mutations in the CYP21A2 gene and is one of the most common monogenic diseases. CAH is characterized by androgen overproduction along with variable degrees of cortisol and aldosterone deficiency. Age at diagnosis can provide some information about the underlying mutations, with those diagnosed at birth/early infancy being at greater risk of developing serious enzyme defects. Classic and non-classical forms of this disorder have been described in the literature. CAH diagnosis is based on the clinical presentation, hormonal panel, Adrenocorticotropic Hormone (ACTH) stimulation test, and genetic testing. The main goals of treatment for congenital adrenal hyperplasia are glucocorticoid/mineralcorticoid supplementation, control of high adrenal androgen levels, fertility control, genetic counseling, and optimization of patients' quality of life.

Purpose of the work: This study aims to review and characterize the clinical and pathophysiological aspects of congenital adrenal hyperplasia.

Materials and methods: A comprehensive analysis of research papers available on PubMed, Google Scholar, Web of Science, Embase and Scopus was undertaken using the search terms encompassing the following keywords: congenital adrenal hyperplasia, 21-hydroxylase deficiency, CYP21A2

Results: Congenital adrenal hyperplasia is a heterogeneous group of genetic disorders that can lead to serious and even fatal complications in the form of adrenal crisis. Therefore, screening tests and early diagnosis are crucial and can save the lives of newborns. Treatment should be individualized and allow patients to achieve normal growth, sexual development, fertility and a better quality of life.

Keywords: congenital adrenal hyperplasia, 21-hydroxylase deficiency, CYP21A2, CAH, glucocorticoid, mineralocorticoid, fertility

Introduction

Congenital adrenal hyperplasia (CAH) is a heterogeneous group of autosomal recessive diseases that impair adrenal steroidogenesis. The most common cause, accounting for 95–99% of cases, is 21-hydroxylase deficiency (21OHD) and is the result of mutations caused by 10 common pathogenic variants in the CYP21A2 gene. The CYP21A2 gene is located in a highly polymorphic region of the major histocompatibility complex (HLA) on the short arm of chromosome 6 at the p21.3 locus, accompanied by the CYP21P pseudogene, with which it has 98% homology. Gene abnormalities vary, ranging from point mutations to large deletions. The clinical phenotype results from the combination of these abnormalities in the two CYP21A2 alleles, with the least affected allele usually determining the phenotype [1,2,3]. Other, much rarer forms of the disease include steroidogenic acute regulatory protein deficiency (STAR), 3-beta-hydroxysteroid dehydrogenase deficiency (3B-HSD), 17-alpha-hydroxylase deficiency, 11-beta-hydroxylase deficiency and cytochrome P450 oxidoreductase deficiency. Deficiency of any of the enzymes necessary for cortisol production causes constant stimulation of the hypothalamic-pituitary system to increase the secretion of corticotropin-releasing hormone (CRH) and corticotropin (ACTH), which stimulate the adrenal cortex, causing its hypertrophy and, in some cases, nodularity. In turn, adrenal hyperplasia, considering their common metabolic pathways, leads to an increase in the synthesis of other steroid hormones. Thus, despite the lack of cortisol biosynthesis, CAH may paradoxically cause adrenal hyperfunction by affecting other steroid pathways [4,5].

CAH is divided into the classic form: salt-wasting (SW)/simple virilization (SV) and the non-classical form. The classic salt-wasting form is the most severe and presents early in life with severe electrolyte imbalance and shock. The classic form with simple virilization manifests with hyperandrogenism, premature puberty, and atypical sexual organs. However, the non-classical type, or late-onset CAH, is similar to the SV type and presents during puberty with hirsutism, oligomenorrhea, or virilization in girls and is sometimes diagnosed during evaluation for infertility or recurrent miscarriages later in life [5]. Newborn screening

for 21OHD is now available in many parts of the world, so most cases of classic CAH are detected in the first week of life, preventing the worst effects of 21-hydroxylase deficiency.

Epidemiology

Overall and individual incidence data are crucial for identifying at-risk populations and improving early detection and management of the disease. Worldwide, CAH (including mild cases) is considered the most common autosomal recessive disorder, surpassing cystic fibrosis and phenylketonuria [4]. Its incidence varies depending on ethnic and geographical factors. Classic CAH is a rare disease with an incidence ranging from 1 in 10,000 to 1 in 16,000 cases [6,7,8]. Previous global studies reported an incidence of classic CAH of 1 in 14,554 live births from 1980 to 1988, and 1 in 5,000 (Saudi Arabia) to 1 in 23,000 (New Zealand) in 1995. A high incidence was observed among Yupik Eskimos in Alaska, USA, due to the founder effect, and on La Reunion Island, France, due to higher rates of consanguinity. Additionally, the incidence in Japan is relatively low compared to North American and European countries. Similarly, CAH was found to be more prevalent in genetically isolated groups and remote geographic regions [9]. Non-classic CAH occurs much more frequently, affecting up to 1 in 200–1,000 people. In some ethnic groups, it is even more common, particularly among Ashkenazi Jews. The prevalence of asymptomatic carriers of classic CAH is 1 in 60, while for non-classic CAH it is 1 in 11 [4,10,11].

Alternatively, CAH incidence can be evaluated based on the type of enzyme deficiency. According to one study, the incidence of 21-hydroxylase deficiency in classic forms ranges from 1 in 10,000 to 1 in 20,000, while for non-classic forms it ranges from 1 in 200 to 1 in 1,000. Among Caucasians, 11β-hydroxylase deficiency is most common (1 in 100,000), and it is also prevalent among Moroccan Jews (1 in 6,000). The incidence of 17α-hydroxylase deficiency is 1 in 50,000, with increased frequency in Brazil. Deficiencies in 3β-hydroxysteroid dehydrogenase and P450 oxidoreductase are rare [9].

Pathophysiology

The adrenal cortex is the main site for steroid hormone synthesis and is organized into distinct layers surrounding the central medulla. The zona glomerulosa (ZG), responsible for producing mineralocorticoids such as aldosterone, is situated just below the capsule that encases the entire gland. Positioned behind the ZG are the zona fasciculata (ZF), which synthesizes glucocorticoids like cortisol in humans and corticosterone in rodents, and the zona reticularis (ZR), which produces adrenal androgens in humans and other mammals. The production of mineralocorticoids is regulated by the renin-angiotensin-aldosterone system, whereas glucocorticoids are managed by the hypothalamic-pituitary-adrenal axis. Glucocorticoids play a role in regulating glucose metabolism, inflammation, immune responses, muscle and bone mass, as well as cognition, well-being, and memory. Mineralocorticoids, on the other hand, are crucial for controlling extracellular fluid volume and sodium homeostasis, thereby significantly affecting blood pressure [2,12,13].

The CYP21A2 gene, located on chromosome 6 (6p21.3), is part of the major histocompatibility complex and resides at a locus with low copy repeats that includes both active genes and pseudogenes. Over 200 mutations in CYP21A2 are known, with most

involving 10 deleterious sequences derived from the nonfunctional CYP21A1P. Deletions account for approximately 20 to 30% of classic CYP21A2 mutations.
Junction sites within these deletions can be clinically significant, as about 3% of them retain partial 21-hydroxylase activity due to their specific location, which is associated with a milder phenotype. Most affected individuals are compound heterozygotes with different mutations on each allele, resulting in a phenotype that corresponds to the milder gene defect. Mutations in the CYP21A2 gene lead to a deficiency in 21-hydroxylase activity (21OHD), which causes reduced cortisol biosynthesis. In severe cases, these mutations may also affect aldosterone production. This lack of cortisol feedback results in elevated ACTH levels, which then lead to the accumulation of 17-hydroxyprogesterone (17OHP) and other steroid precursors, contributing to excess androgen production. Allelic variants of CYP21A2 are linked to a spectrum of enzyme phenotypes. As CAH is a recessive genetic disorder, affected individuals can be either homozygous (with the same mutation present in both alleles) or compound heterozygous (with different mutations in each allele) [4,14].

In the adrenal cortex, the fate of newly synthesized pregnenolone is determined by the levels of downstream enzymes. In the absence of 21-hydroxylase, cortisol precursors are redirected to produce androgen precursors. A portion of 17-hydroxyprogesterone is converted into 21-deoxycortisol, which is exclusively produced in the adrenal glands and not in the gonads, unlike 17-hydroxyprogesterone. Consequently, 21-deoxycortisol is a more specific biomarker for 21-hydroxylase deficiency compared to 17-hydroxyprogesterone and is thus included in some newborn screening protocols. Additionally, androstenedione, which is a good substrate for 11-hydroxylase, is converted into 11β-hydroxyandrostenedione, the most abundant androgen precursor in nearly all patients with 21-hydroxylase deficiency. Extra-adrenal metabolism then converts 11β-hydroxyandrostenedione into 11-ketotestosterone, a potent androgen receptor agonist [1,15].

Reduced cortisol production disrupts the feedback mechanism of the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased production of corticotropin-releasing factor (CRF) in the hypothalamus and adrenocorticotropic hormone (ACTH) in the pituitary gland. The resulting low cortisol levels in the adrenal glands during development cause adrenal medullary dysplasia and adrenal insufficiency. Although the renin-angiotensin-aldosterone system is not directly influenced by ACTH, the volume deficiency resulting from aldosterone deficiency provides an additional stimulus for ACTH production, which indirectly stimulates vasopressin synthesis in the hypothalamus. Co-secreted with CRF, vasopressin works synergistically with CRF to enhance ACTH release. ACTH signaling through the melanocortin receptor type 2 (MC2R) drives adrenal steroidogenesis and acts as a trophic factor for the adrenal glands. Excess ACTH leads to adrenal cortex hypertrophy and uncontrolled synthesis of adrenal androgens and androgen precursors, including 17-hydroxyprogesterone (17-OHP) and androstenedione, which are traditional biomarkers for CAH. This accumulation of androgen precursors and hyperactivity of the HPA axis results in a tendency for overproduction of androgens in the adrenal glands affected by CAH [4,15,16].

Symptoms

Although CAH is a monogenic disease, the phenotypic manifestations are highly variable. Based on clinical symptoms and their severity, CAH is divided into classic and non-classic forms.

In the classical form, there is a salt loss form and a simple virilization form, although this division becomes less important because in both cases salt loss occurs to some extent [4]. Approximately 10% of patients have CAH-X syndrome, which is characterized by features of CAH in combination with features of Ehlers-Danlos syndrome. The CYP21A2 gene partially overlaps with a gene that affects collagen deposition, tenascin-XB (TNXB), so CYP21A2 deletions that extend into TNXB cause CAH-X. Clinically, patients present with hypermobility, joint pain and dislocations, hernias, and midline defects that may include structural cardiac abnormalities, in addition to symptoms associated with CAH [7,14].

Salt Wasting Classic CAH

This form of the disease is the result of complete or almost complete lack of activity of the P450c21 enzyme (<1%). There is a severe deficiency of aldosterone and cortisol, which can lead to a salt wasting crisis in newborns. In the absence of early diagnosis and treatment (now made possible by newborn screening programs), infants with salt-wasting CAH develop life-threatening adrenal crises within the first 2 weeks of life [16]. Affected individuals typically present with adrenal insufficiency associated with hypovolemic shock, hyponatremia, hyperkalemia, metabolic acidosis, and sometimes hypoglycemia. Children experience a lack of weight gain, poor appetite, signs of dehydration, vomiting, drowsiness, and deterioration of their general condition. Most often, this does not occur within 5 days of birth; symptoms usually appear when newborns are discharged from the hospital. Therefore, SW-CAH requires high diagnostic suspicion, especially in males due to the lack of ambiguity of the genital organs. Excess androgens starting before birth are particularly unfavorable for girls, causing irreversible changes in the external genital organs during their formation. Although the uterus, fallopian tubes, and ovaries form normally, clitoral hypertrophy, fusion of the labia, and defects of the urogenital sinuses may occur. This may cause difficulties in determining the sex of the newborn immediately after birth and often leads to incorrect determination of the sex as male in an affected girl. There is great diversity among patients, as indicated by the Prader classification, ranging from 1 to 5, where grade 1 is characterized by mild clitoral hypertrophy and grade 5 by complete masculinization. Boys with classic CAH are born with normal genitalia (although hyperpigmentation of the external genitalia may be present), which means that, even despite typical symptoms of salt-wasting syndrome, diagnosis of the disease and initiation of appropriate treatment are often delayed. Inflammatory diseases of the gastrointestinal tract, pyloric stenosis, or other causes of weight deficiency are suspected in such newborns [4,10,17].

Simple Virilizing CAH

This form of the disease is associated with CYP21A2 mutations that retain <5% enzymatic activity and some ability to produce aldosterone. The condition is usually detected before puberty, typically at 1 year of age or in early childhood. It is characterized by

symptoms such as hyperandrogenism, premature puberty, and the appearance of pubic/axillary hair, apocrine odor, and an enlarged clitoris.

Untreated children with this form of the disease grow rapidly, their bone age is disproportionately advanced, and as a result, their final height is low.

Tumorous changes in the testicles are also quite common symptoms of CAH in pubertal boys. Most patients have subclinical cortisol deficiency, but mineralocorticoid function is preserved [4,10,17].

Non-classical CAH

The non-classical (mild) form is associated with CYP21A2 mutations that retain 20 - 50% of enzyme activity. This form may be asymptomatic and is quite common. Unlike the classic form, in this case, the concentrations of cortisol and aldosterone in patients remain unchanged. The most common reason for consulting patients is late-onset hyperandrogenism, usually appearing in the peri-pubertal period or in adulthood. This condition is significantly underdiagnosed among men due to the difficulty in assessing hyperandrogenism. In girls, the most common reasons for medical consultation are premature pubic hair, hirsutism, severe acne, and menstrual disorders. The clinical picture of this form in girls often resembles the symptoms of polycystic ovary syndrome, although the coexistence of both diseases as a consequence of chronic hyperandrogenism in the course of CAH cannot be ruled out. The disease is often diagnosed later in life, even in adulthood, in the context of infertility research or after recurrent miscarriages [4,10,17].

Diagnostics

Due to the nature of the disease, CAH can be diagnosed using various diagnostic techniques:

- Hormonal diagnostics (including neonatal screening tests)
- Biochemical diagnostics
- Genetic testing
- Prenatal diagnostics
- Imaging studies

- **Hormonal diagnostics and biochemical diagnostics**

The first test that allows for detecting the disease at a very early stage is a newborn screening test. A dried blood spot, usually taken on the 3rd to 5th day of life, is tested to assess the level of 17-OHP to detect 21-hydroxylase deficiency. The primary challenge with this screening is a high false positive rate, especially in preterm or stressed infants who naturally have elevated 17OHP levels. Additionally, false negatives may occur due to factors like antenatal corticosteroid use, and the timing of screening impacts diagnostic accuracy. 17-OHP standards depend on the duration of pregnancy and birth weight and positive results must be verified by performing additional tests. Despite the high specificity and sensitivity of neonatal screening for 21-hydroxylase deficiency (21OHD), the positive predictive value is low due to the rarity of the disease. A second-tier screen, such as direct biochemical analysis using LC-MS/MS, can improve specificity by addressing immunoassay limitations.

Measuring steroid ratios or specific steroids like 21-deoxycortisol can further enhance diagnostic accuracy.

In children not included in the screening test, whose clinical picture or test results suggest suspicion of CAH, the following tests can be performed:

- 17-OHP, testosterone, ACTH, cortisol, ARO (plasma renin activity), aldosterone, in blood serum
- 24-hour urine steroid profile collection (high level of pre-enzyme block metabolites and low level of end products of impaired steroidogenesis)
- ACTH test (measuring ACTH, cortisol, and 17-OHP)
  In this test, the patient receives a bolus of ACTH, and levels of 17-OHP and cortisol are measured at 0 and 60 minutes. In patients with the classic form of 21-hydroxylase deficiency, both basal and stimulated 17-OHP concentrations are significantly elevated. Basal 17-OHP levels typically exceed 20 ng/ml and increase to >50–100 ng/ml following ACTH stimulation. Patients with milder, non-classical forms of the disease usually exhibit normal or slightly elevated basal 17-OHP levels, with a significant rise after ACTH stimulation. In patients with classic CAH, the ACTH test also reveals a low cortisol reserve, whereas in those with non-classic forms, the cortisol reserve remains normal. Basal ACTH levels indicate the extent of 21-hydroxylase and cortisol deficiencies, with significant elevations seen in severe cases of CAH, while levels may be normal in milder forms without adrenal insufficiency [2,10,17].

Important biochemical tests are: ionogram (Na+, K+, Cl–) in serum, glycemia, acid-base balance in serum [17].

Parameter	**Type 1 (CAH with 21-Hydroxylase Deficiency)**	**Type 2 (CAH with 11-Hydroxylase Deficiency)**	**Type 3 (CAH with 17-Alfa-Hydroxylase Deficiency)**
Cortisol	Low or decreased levels	Low or decreased levels	Low levels
Aldosterone	Low levels	Increased levels	Increased levels
Androstenedione	Increased levels	Increased levels	Low levels
17-Hydroxyprogesterone	Increased levels	Normal or decreased levels	Low levels
Testosterone	Increased levels	Increased levels	Low levels

K+ (Potassium)	Increased levels (hyperkalemia)	Increased levels (hyperkalemia)	Normal or low levels
Na+ (Sodium)	Low levels (hyponatremia)	Low or decreased levels	Normal or decreased levels

Table 1: Hormonal and Electrolyte Profiles in Different Types of CAH
This table compares the key parameters among three types of CAH: Type 1 (21-Hydroxylase Deficiency), Type 2 (11-Hydroxylase Deficiency), and Type 3 (17-Alpha-Hydroxylase Deficiency). It outlines the typical levels of cortisol, aldosterone, androstenedione, 17-hydroxyprogesterone, testosterone, potassium (K+), and sodium (Na+), highlighting the variations in hormone and electrolyte imbalances associated with each type [4,17,18].

- **Genetic testing**

Each patient with CAH should receive genetic counseling. In children with CAH who also have disorders of sexual development, karyotype analysis is essential, particularly before planning any surgical treatment. A deficiency in 21-hydroxylase is the most common cause of sexual development disorders in patients with a 46,XX karyotype (46,XX DSD). Karyotype analysis helps exclude other possible causes of these disorders.

In cases of children with typical clinical and hormonal presentation of CAH, molecular testing, such as identifying mutations in the CYP21A2 gene, is not required for diagnosis. However, molecular analysis is useful in challenging diagnostic cases and is necessary for planning prenatal diagnosis and treatment [10,17].

- **Prenatal diagnostics**

Routine fetal diagnostics for congenital adrenal hyperplasia (CAH) are generally not conducted unless there is a family history of the disease. Prenatal diagnostics for 21-hydroxylase deficiency typically involve measuring fetal 17-OHP or androstenedione levels in amniotic fluid. However, these steroid levels may not be elevated in cases of non-classical CAH or classical CAH without salt loss. If a family already has a child with CAH, HLA typing can be performed on fetal amniocytes. Additionally, fetal gene sequencing may be utilized when the mutation occurring in the family is known [17].

- **Imaging studies**

In patients with symptoms of adrenal insufficiency, including congenital adrenal hyperplasia (CAH), imaging studies such as ultrasound (US) or computed tomography (CT) of the adrenal glands are performed for differential diagnosis. Pelvic ultrasound is essential for assessing the internal reproductive organs in children with developmental abnormalities of the genitalia. Ultrasound is also used to evaluate the testes in boys with CAH due to the potential presence of nodular changes in the gonads. Additionally, wrist X-rays are necessary to assess bone age and provide a means to monitor hormonal treatment [10].

Differential Diagnosis

Differential diagnosis should encompass all forms of congenital adrenal hyperplasia (CAH) as well as the entire group of disorders of sexual development. CAH is considered one of the most common causes of sexual differentiation disorders in newborns.

- An infant with abnormal genitalia should be closely monitored for several days to weeks after birth to detect signs of salt-wasting syndrome, as it may not be immediately evident.

  Dehydration symptoms in a newborn initially identified as a boy but with bilateral cryptorchidism could suggest salt-wasting syndrome in a girl with CAH, due to significant masculinization of the genitalia resulting in an incorrect gender assignment.
- Salt-wasting syndrome, especially in boys during the first weeks of life, should be differentiated from congenital adrenal hypoplasia and adrenal insufficiency from other causes like bilateral adrenal hemorrhages.
- In an infant with electrolyte and gas abnormalities similar to those seen in salt-wasting syndrome but without pronounced signs of hyperandrogenization, conditions such as pseudohypoaldosteronism, renal tubular acidosis, and obstructive uropathy must be ruled out.
- In children older than one year, signs of hyperandrogenization - such as the early appearance of pubic hair (before age 8), rapid growth, advanced bone age, and, in boys, accelerated genital development - must be distinguished from true precocious puberty and hormonally active adrenal or gonadal tumors.
- In older girls, an ultrasound should be performed to assess ovarian structure and internal genitalia, and hormonal tests should be conducted to differentiate CAH (particularly non-classical forms) from functional disorders or polycystic ovary syndrome (PCOS) [10].

Treatment

The treatment of congenital adrenal hyperplasia involves the substitution of glucocorticoids and mineralocorticoids in the classical form and glucocorticoids alone in symptomatic cases of the non-classical form. Glucocorticoid therapy suppresses excess CRH and ACTH, consequently reducing androgen secretion by the adrenal cortex [2].

In the chronic therapy of congenital adrenal hyperplasia in children, hydrocortisone is administered at a dose of 12-18 mg/m² body surface area, divided into 3-4 doses per day (in neonates, doses can reach 25-30 mg/m²). The doses used in older children and adolescents are increased due to the accelerated metabolism of cortisol during puberty. After the growth process is complete, hydrocortisone can be replaced with another, longer-acting glucocorticoid such as prednisone or prednisolone, which are administered in 2, instead of 3, doses per day. In cases of salt-wasting syndrome, additional mineralocorticoid therapy is necessary. Fludrocortisone is administered at a dose of 0.05-0.15 mg/24 hours, depending on the results of control tests. In the first year of life, additional NaCl supplementation (1-3 g/24 hours) is usually indicated. In stressful situations such as infections with fever, trauma, surgical procedures, or general anesthesia, the dose of hydrocortisone should be increased 3-4 times for 1-2 days. This will prevent the development of full-blown acute adrenal insufficiency.

There is no need to increase the dose of fludrocortisone in such cases, as hydrocortisone also has mineralocorticoid activity. If oral administration of medication is not possible, for example, due to persistent vomiting, it is necessary to administer the medication parenterally - either intramuscularly or intravenously [4,10]. It is crucial to maintain a balance between too low and too high doses of steroids administered in supraphysiological amounts. Excessive doses of glucocorticoids (GKS) can lead to growth suppression and may induce iatrogenic Cushing's syndrome.

On the other hand, insufficient doses of GKS will cause excessive production of adrenal androgens and symptoms of hyperandrogenization, as well as rapid growth with disproportionate acceleration of bone age, ultimately resulting in reduced final height. Overdose of mineralocorticoids (MKS) can lead to hypertension and its complications, while too low a dose can cause salt-wasting syndrome, which results in vomiting, diarrhea, metabolic acidosis, hyponatremia, and hyperkalemia. [15] Treatment for congenital adrenal hyperplasia is typically managed at pediatric endocrinology clinics. Emergency situations should be directed to the nearest pediatric department, as they are at risk of adrenal crisis. Replacement therapy does not contraindicate vaccinations. Currently, several studies are underway to develop alternative therapeutic approaches. These include trials involving corticotropin-releasing hormone (CRH) receptor antagonists, melanocortin-2 receptor (MC2R) antagonists, adrenolytic agents, and corticotropin antibodies [19].

In girls with signs of masculinization, surgical correction of the external genitalia is essential, preferably during infancy. Such treatment should be performed at surgical centers with extensive experience in managing disorders of sexual differentiation. Masculinization does not affect the internal genital organs. Girls receiving appropriate treatment can menstruate and plan for childbirth. In boys, proper treatment does not prevent changes in the gonads. The incidence of testicular adrenal rest tumors (TARTs) can be as high as 20% among children and between 50% and 80% in adults with classic congenital adrenal hyperplasia. Experts recommend that boys with classic CAH undergo testicular ultrasound starting at age 8 and have follow-up examinations every 2 years. Treatment of TARTs involves optimal pharmacological management. Surgery is indicated only in cases of severe pain, as it does not improve fertility restoration in men [4,20,21].

Long-term Sequelae

Cardiovascular and metabolic complications

Studies show that patients with congenital adrenal hyperplasia have an increased cardiovascular and metabolic risk. In a study conducted in the Swedish cardiovascular disease registry, hypertension, hyperlipidemia, atrial fibrillation, venous thromboembolism, obesity, obstructive sleep disorders, and diabetes were more common in patients with CAH compared to matched controls. Hypertension is higher in Salt Wasting CAH patients than in Simple Virilizing CAH patients [22]. In adolescent and adult CAH patients, normal left ventricular morphology has been reported, but mild diastolic dysfunction and impaired exercise capacity have been demonstrated [2]. In patients treated with glucocorticoids, increased carotid intima-media thickness and insulin resistance occur. In addition, there is a risk of developing iatrogenic Cushing's syndrome.

Furthermore, women with classic CAH have an increased risk of gestational diabetes compared with age-matched controls, which carries a risk of developing diabetes later in life [7,14].

Bone health

The main cause of long-term effects related to decreased bone density and osteoporosis and consequently increased risk of bone fractures in patients with CAH is the lifelong use of glucocorticoids. In addition, glucocorticoids can cause secondary hyperparathyroidism by reducing intestinal calcium absorption and increasing renal calcium excretion [2]. Most studies have confirmed that glucocorticoids cause a decrease in BMD at at least one of the measured sites in both sexes and in all age groups, although some studies have shown normal or even high BMD. These differences may be due to both glucocorticoid and androgen exposure, as androgens stimulate osteoblast proliferation and differentiation in both sexes. Furthermore, patients with classic CAH have poorer BMD compared with patients with nonclassical CAH [7].

Neurological aspects

The imbalance in androgen and glucocorticoid exposure characteristic of CAH may affect the development of neural circuits and brain function, and potentially affect mental health. Patients with classic CAH, compared with controls, have a higher incidence of anxiety, depression, alcohol abuse, suicidal ideation, and adjustment disorders. Women with the most severe genotype and men diagnosed after the neonatal period are particularly at risk for mental health problems. Neuroimaging studies in affected patients have revealed changes in brain structure and function. In a functional MRI study of 14 adolescents with classic CAH, compared with age-matched controls, girls with CAH showed a similar pattern of amygdala activation to boys in the control group, suggesting an effect of androgens on amygdala function in girls with CAH [1]. Studies have shown that glucocorticoid therapy for CAH affects working memory and digit span performance. Patients who took higher doses of glucocorticoids had worse outcomes in this regard. Young people with classic CAH had smaller regional volumes in the prefrontal cortex, amygdala, and hippocampus and smaller brain volumes overall than age-matched controls. CAH is associated with multiple hormonal imbalances, including glucocorticoid deficiency and androgen excess in utero, postnatal androgen excess, iatrogenic glucocorticoid excess, and epinephrine deficiency, all likely occurring at different developmental times and with different potential effects on neural circuits [2].

Adrenal tumors

Adrenal tumors occur in up to 20% to 30% of adult patients with CAH. In a meta-analysis, 0.8% of all incidental adrenal tumors were due to previously undiagnosed genetic

CAH [7]. Almost 25% of these are benign adrenal myelolipomas, which occur most often in patients with poor hormonal control. This suggests that excessive ACTH stimulation may play a role in pathogenesis. Thus, increased glucocorticoid therapy may reduce the size of adrenal tumors in the early stages, whereas bilateral adrenalectomy may increase the size. 17-hydroxyprogesterone levels correlate with adrenal tumor size. Testicular adrenal residual tumors (TARTs) are common in the testes of men with CAH. They occur not only in 21OHD but also in 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase type 2 deficiencies.

They occur with a frequency of about 40%, have a histological similarity to adrenal cortex cells, are thought to arise from abnormal adrenal cells in the testes, are usually bilateral and painless, although in the case of extensive tumors there may be discomfort. The central location of TART in the testes may result in mechanical obstruction of the seminiferous tubules with azoospermia and irreversible peritubular fibrosis. In addition, the paracrine action of steroids produced by TART may destroy the surrounding Sertoli cells or germ cells. Residual ovarian tumors, on the other hand, are less common or rarely reported, probably because of their location in the abdominal cavity, where the use of ultrasonography is not optimal [2,7].

Autoimmune disorders

Since the CYP21A2 gene is located in a highly immunologically active region, it would be reasonable to assume that 21-hydroxylase deficiency would have an impact on autoimmune disorders. On the other hand, most patients require glucocorticoid replacement therapy, which in turn has an immunomodulatory effect. In a study of 145 patients with CAH, 3.4% had a comorbid autoimmune disorder, whereas in a pan-European study of disorders of sexual development, 22.2% of 222, mostly female patients with CAH, had a comorbid autoimmune disorder [7]. The most common disease in both sexes was autoimmune thyroid disease.

Fertility

Both sexes with CAH have gonadal dysfunction. In women, it may be caused by high levels of adrenal androgens and steroid precursors, polycystic ovary syndrome, or rarely by residual ovarian tumors. In pubertal girls and women, this may cause abnormal pubertal development, irregular menstruation, or amenorrhea. 17-hydroxyprogesterone and progesterone bind to the progesterone receptor, which affects ovulation, as well as endometrial and cervical mucus function. Patients may develop hypogonadotropic hypogonadism, caused by high levels of androgens and by supraphysiological glucocorticoid replacement. Compared with age-matched controls, women with CAH have fewer pregnancies and fewer children. Factors such as virilized genitalia and subsequent genital surgery, decreased sexual activity, decreased interest in infants, lack of a partner, decreased sexual satisfaction, and genitourinary and sexual dysfunction as a result of corrective surgery may also affect the desire and ability to become pregnant. In men with CAH, primary gonadal dysfunction may be caused, as in women, by secondary hypogonadotropic hypogonadism, but

also by TART. Men with CAH are also less sexually active compared with matched controls, so that in men, fertility rates are also markedly reduced [2,7].

Conclusions

Congenital adrenal hyperplasia is a widespread and heterogeneous group of genetic disorders. It can occur in childhood, adolescence and adulthood. Early diagnosis of the classic salt-wasting form is very important and can save the life of the newborn, while early diagnosis of the non-classical form can significantly improve the quality of life of patients. Measurement of 17-OHP level is used in newborn screening tests and in diagnostics. More sensitive and specific analytical techniques are used to confirm the results.

Therapy should be individualized, tailored to the needs of the individual patient, so that they can achieve normal growth, sexual development, fertility and a better quality of life. CAH, due to its complex nature and treatment, can result in many negative consequences in the future, therefore regular monitoring of risk factors and complications is essential to be able to implement support and treatment in a timely manner.

Disclosure:

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