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Congenital adrenal hyperplasia due to 21-hydroxylase deficiency – management and differentiation in adults

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ABSTRACT

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive hereditary diseases. The lack of cortisol synthesis leads to excessive stimulation of the adrenal glands by adrenocorticotrophic hormone (ACTH). Moreover the impairment of cortisol synthesis results in adrenal hyperplasia and excessive androgen synthesis. Congenital adrenal hyperplasia is characterised by a considerable correlation between the genotype and the phenotype with the type of *CYP21A2* gene mutation affecting the severity of 21-hydroxylase deficiency. The clinical manifestations of congenital adrenal hyperplasia in adults result from adrenocortical insufficiency, hyperandrogenism, and the adverse effects of glucocorticosteroids, which are used for the treatment of the syndrome. Non-classic congenital adrenal hyperplasia may sometimes have no clinical manifestation. Patients with classic congenital adrenal hyperplasia experience a wide variety of symptoms, including obesity, hypertension, hyperinsulinaemia, insulin resistance, and hyperleptinaemia. These abnormalities, the same as glucocorticosteroid treatment, promote the development of other diseases, such as metabolic syndrome, diabetes mellitus, cardiovascular diseases and psychosocial problems. Moreover glucocorticosteroids treatment increases risk of osteoporosis and dermatological disorders. The maladies are more often seen in patients suffering from congenital adrenal hyperplasia syndrome than in the general population. Patients suffering from congenital adrenal hyperplasia require systematic evaluation of biochemical parameters (17-hydroxyprogesterone and androstendion) the same as clinical parameters (body mass index, waist circumference, glucose, lipids, blood pressure). Medical care for patients suffering from congenital adrenal hyperplasia should be

provided by reference centres. Patients require cooperation between an endocrinologist, diabetologist, gynaecologist, andrologist, urologist, sexuologist and psychologist.

Keywords: congenital adrenal hyperplasia, 21-hydroxylase, androgens, glucocorticosteroids

1. INTRODUCTION

Congenital adrenal hyperplasia (CAH) is one of the most common autosomal recessive hereditary disease. 90-95 percent of cases of CAH is a result of 21-hydroxylase deficiency, the enzyme encoded by the CYP21A2 gene [1-5]. The role of 21-hydroxylase is to converse 17-hydroxyprogesterone to 11-deoxycortisol. Mutations in the CYP21A2 gene cause the cortisol deficiency and, in more progressive form, aldosterone deficiency.

Moreover, a higher amount of ACTH is released, leading to excessive production of 17-hydroxyprogesterone (17-OHP). This steroid undergoes inordinate conversion to androgens, hormones which plethora cause clinical manifestation of the syndrome. Depending on the severity of 21-hydroxylase deficiency three main types of congenital adrenal hyperplasia (CAH) are identified [1]:

- **Classic salt-wasting congenital adrenal hyperplasia (SW CAH)** – total lack of 21-hydroxylase activity, leading to cortisol and aldosterone deficiency.
- **Classic simple virilizing congenital adrenal hyperplasia (SV CAH)** – only 1-2% of 21-hydroxylase activity is maintained. The clinical picture shows cortisol insufficiency, in contrast to aldosterone, which concentration and function are preserved.
- **Non-classic congenital adrenal hyperplasia (NC CAH)** – 20-50 % of 21-hydroxylase activity is preserved. The onset of this form occurs in late childhood or during puberty. Mild androgen excess is characteristic for NC CAH.

2. EPIDEMIOLOGY

The frequency of occurrence of congenital adrenal hyperplasia was based on neonatal screening. Data from approximately 6.5 million newborn infants screened worldwide to show the mean prevalence of classic CAH approx. 1 in 15,000 live births. [2, 6, 7] Spread differs according to ethnicity and geographic area. This number varies from as low as 1 in 28,000 in the Chinese population [8], 1 in 5000 to 23,000 live births in Caucasian [9, 10], to as high as 1 in 280 in Yupik Eskimos in Alaska [11] and 1 in 2100 in the French island of La Reunion. [7] In the United States, the prevalence is lower in African Americans than in Caucasians (1 in 42,000 versus 1 in 15,500, respectively). [12]

Approximately 67 percent of classic congenital adrenal hyperplasia patients are classified as "salt-losing," (SW CAH), while 33 percent of classic adrenal hyperplasia patients have "non-salt-losing" or the "simple virilizing" form (SV CAH) reflecting the degree of aldosterone deficiency. [6]

The non-classic congenital adrenal hyperplasia (NC CAH) is more common (about 1 in 1000 cases) [1, 12] and the frequency depends on the ethnicity. Among Caucasians, the

prevalence of NC CAH may be as high as 1 in 1000 to 1 in 100 [2, 11, 13, 14], with the spread being significantly higher among Mediterranean, Hispanics, Yugoslavs, and Eastern European Jews. It is important to highlight that most patients with the non-classic form can not be diagnosed by standard screening studies, because they are based upon detection of very high levels of 17-hydroxyprogesterone [15]

3. PATHOPHYSIOLOGY

The hallmarks of 17-hydroxyprogesterone, first described in 1966 [16, 17], include hypertension and hypokalemia due to the accumulation of cortisol precursors with mineralocorticoid activity upstream of the block, plus sexual infantilism due to inability to synthesize androgens and estrogens.

Congenital adrenal hyperplasia results mostly from deficiency of 21-hydroxylase, enzyme which converses 17-hydroxyprogesterone to 11-deoxycortisol. It leads to reduced cortisol synthesis and therefore increased corticotrophin (ACTH) secretion (Figure 1). In this way adrenal glands are stimulated to growthed production of androgens. The severity of disease relates to the grade to which the mutations compromise enzyme activity [18].

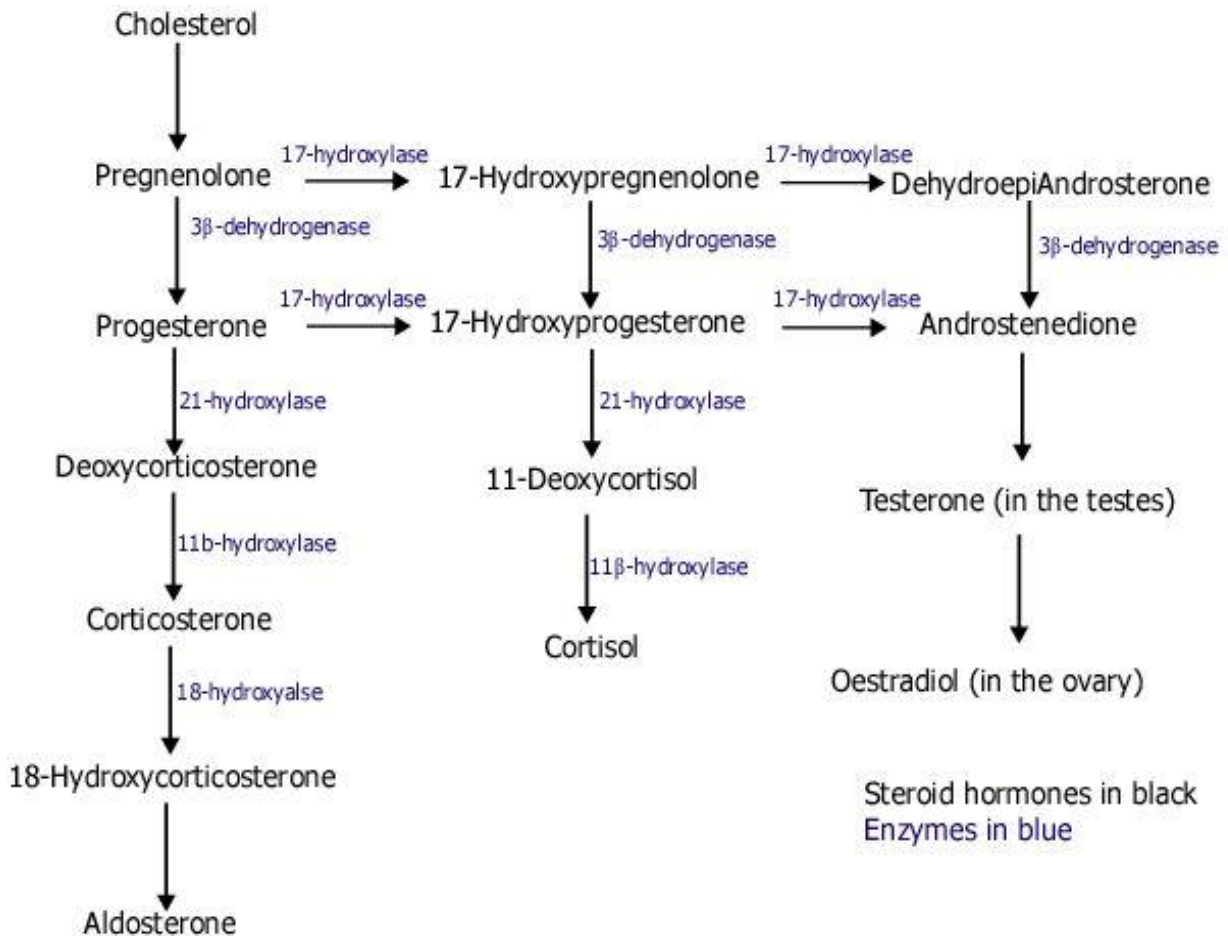


Figure 1. Pathways of adrenal steroid synthesis.

4. CLINICAL MANIFESTATION

The clinical spectrum of classic forms of congenital adrenal hyperplasia ranges from the mild to the most severe forms, depending on such factors as adrenocortical and adrenomedullary insufficiency, androgen excess, individual sensitivity to androgens and the adverse effects of medicines used for the treatment of CAH.

4. 1. Manifestations of adrenocortical insufficiency

Adrenocortical insufficiency is diagnosed in patients with classic congenital adrenal hyperplasia. Patients with classic-salt wasting CAH (SW CAH) may be apathetic and show general malaise, easy fatigability, loss of appetite and weight loss. Symptoms such as abdominal pain, nausea, vomiting, diarrhoea, myalgia and low blood pressure indicate an early adrenal crisis, which is a potentially life-threatening situation requiring immediate emergency treatment. Moreover, some patients suffering from classic- salt-wasting CAH (SW CAH) present with skin lesions, for instance, hyperpigmentation [1].

Patients with classic congenital adrenal hyperplasia also present insufficient level of hormones produced in adrenal glands medulla. It is associated with the abnormal formation of the adrenal medulla during the prenatal period. Patients with CAH have lower levels of plasma adrenaline, methoxy adrenaline and urinary adrenaline compared to control group [1, 20]. Adrenaline and cortisol deficiency increases the risk of severe hypoglycemia, especially in situations of growth requirement for adrenal cortex hormones [1, 21].

4. 2. Dermatological symptoms and reproductive system manifestations

Women suffering from congenital adrenal hyperplasia present with various gynaecological endocrinology symptoms. Higher androgens levels (hyperandrogenism) may cause hirsutism, acne, androgenetic alopecia, insufficient development of the breasts and menstrual disorders.

Hirsutism is defined as the presence of terminal coarse hairs in female skin a male-like distribution [22]. The Ferriman- Gallwey score is a method of evaluating and quantifying hirsutism in women [23] (Figure 2).

Androgenetic alopecia, also known as male-pattern baldness, female-pattern baldness, is the most common type of progressive hair lose [24]. In women, hair lose or thinning occurs at the crown of the scalp, with complete or nearly complete preservation of the frontal hairline [24, 25] (Figure 3).

About 40% of women with classic salt-wasting congenital adrenal hyperplasia (SW CAH) and 20% of women with classic simple virilizing congenital adrenal hyperplasia (SV CAH) suffer from fertility problems [1, 26]. Causes of decreased fertility are composite. Exposure of the fetus to the high concentrations of androgens during prenatal period may interfere with the development of the hypothalamic-pituitary-gonadal axis. Increased levels of progesterone, 17-hydroxyprogesterone and androgens have a negative impact on the reproductive system [1, 4, 21, 27, 28].

Furthermore, women with congenital adrenal hyperplasia often suffer also from polycystic ovary syndrome (PCOS) and insulin resistance, which increase the risk of anovulation cycles. In addition, women diagnosed with classic CAH have sex life problems.

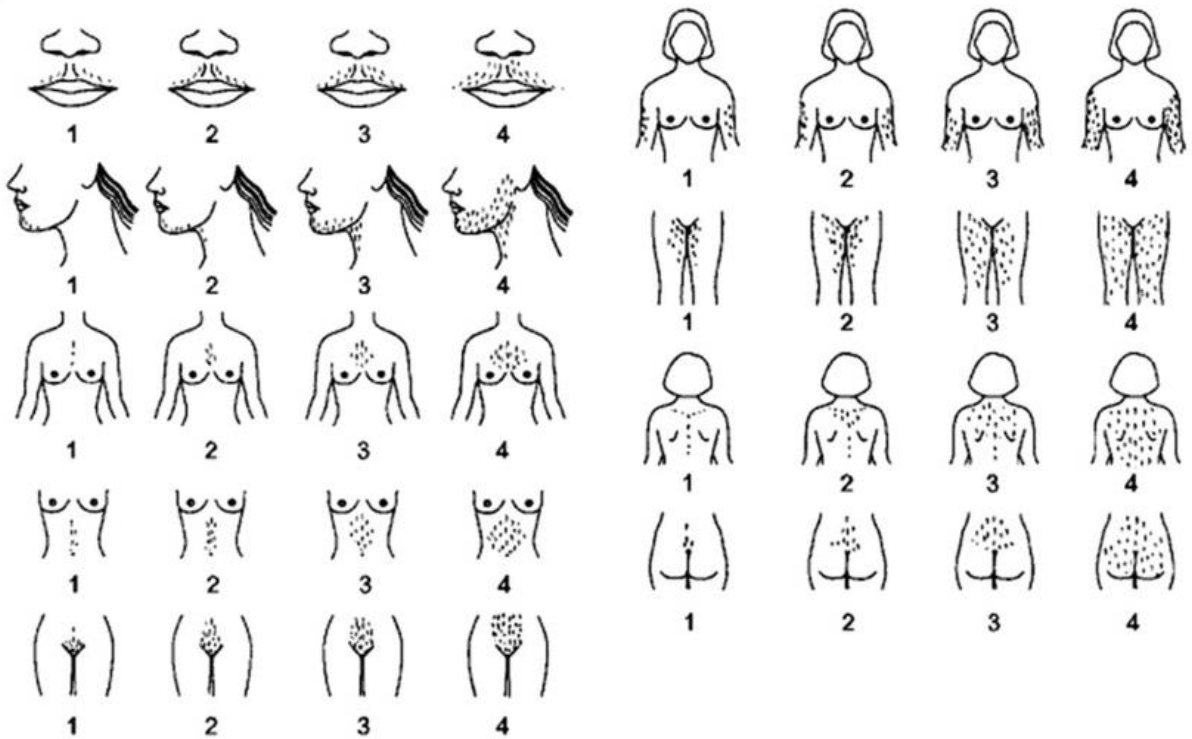


Figure 2. Ferriman - Gallwey score [23].



Figure 3. Androgenetic alopecia.

Abnormal anatomical structure of the external genitals causes pain in the pelvis and bleeding during sexual intercourse, frequently resulting in post-intercourse dissatisfaction and subsequently lose their interest in sex life [1]. Men suffering from congenital adrenal hyperplasia, similarly to women, are at higher risk of infertility. It is caused by testicular adrenal

rest tumour (ART), LH suppression and co-existence of metabolic syndrome and insulin resistance. It is recommended, for men suffering from CAH, to test their semen at 3- to 5- year intervals [1] and prescribe glucocorticosteroids in order to improve the quality of semen and fertility [1, 29, 30].

4. 3. Manifestations of non-classic congenital adrenal hyperplasia

Clinical manifestation of non-classic congenital adrenal hyperplasia appear lately, mostly during growing up period or adulthood. Manifestations of NC CAH in adult women include hirsutism, acne, frontal alopecia, oligomenorrhoea, infertility and virilisations symptoms (clitoromegaly, male pattern hair growth, deepening of the voice). The causes of infertility are similar to those in the classic forms of congenital adrenal hyperplasia and affect about 13 % of women with NC CAH [1, 31].

4. 4. Adrenal tumours

Patients suffering from classic forms of CAH and non-classic CAH are at higher risk of appearance of unilateral or bilateral focal changes in the structure of adrenal glands [1, 32]. Treatment with glucocorticoids may decrease in size the adrenal tumours. It is important to examine the patients suffering from congenital adrenal hyperplasia for adrenal tumours. Likewise, patients diagnosed with adrenal tumours should be examined for congenital adrenal hyperplasia [1].

4. 5. Height and bone mineral density

Early exposure to androgens and accelerated growth rate in childhood cause the lower growth in adult life in patients with congenital adrenal hyperplasia [1, 33].

Moreover, treatment of congenital adrenal hyperplasia with glucocorticoids can lead to reduced bone mineral density (BMD) resulting in osteoporosis thus increasing the risk of bone fracture [1, 34]. In order to reduce the risk of osteoporosis development physician should apply low doses of glucocorticoids. Furthermore, nutrition has also a significant impact on reducing the frequency of osteoporosis. In this setting, Calcium and Vitamin D3 rich diet and supplementation in combination with appropriate physical activity are recommended.

4. 6. Metabolic syndrome

Classic congenital adrenal hyperplasia significantly increases the risk of metabolic syndrome. The patients diagnosed with CAH present increased body fat, increased incidence of overweight or obesity, insulin resistance and higher insulin levels [1, 35, 36].

Metabolic disorders in patients with CAH result from periodic hypercortisolemia, insufficiency of the adrenal medulla and hyperandrogenism [1, 20]. Treatment of systemic glucocorticosteroid promotes elevated levels of cortisol and in the same way – obesity. Deficiency of adrenaline, hormone produced in the adrenal medulla, also leads to obesity, by causing hyperinsulinemia, insulin resistance, hyperleptinaemia, impaired thermogenesis and lipolysis [1, 37]. As a result, these patients suffer from dyslipidemia, abnormalities of carbohydrate metabolism (impaired fasting glucose, impaired glucose tolerance, diabetes mellitus) hypertension and increased risk of cardiovascular diseases (for instance myocardial infarction). Combination of healthy, well-balanced diet and physical activity may also reduce cardiovascular risk in this group of patients.

4. 7. Psychosocial problems

Patients suffering from congenital adrenal hyperplasia have the considerably lower quality of life in comparison to healthy individuals. Psychosocial problems in women with CAH result from hyperandrogenism, especially from the effects of androgens on central nervous system functions. These patients often live a solitary life, have low self-esteem and are less sexually active. It results in lack of satisfaction during sexual intercourse and lowers their interest in this aspect of life. Sexual orientation also varies from controls [38]. Studies show that women suffering from congenital adrenal hyperplasia present more often homosexual and bisexual behaviour than healthy women.

5. DIAGNOSTIC APPROACH IN CONGENITAL ADRENAL HYPERPLASIA

Appropriate diagnosis of congenital adrenal hyperplasia should firstly aim to determine the form of the disease that concerns the given patient. This is based on a clinical picture with correlation to laboratory findings [38].

5. 1. Diagnosis of classic forms of congenital adrenal hyperplasia

The diagnosis of classic forms of congenital adrenal hyperplasia to 21-hydroxylase deficiency (21OHD) is based on very high serum concentration of 17-hydroxyprogesterone (17OHP), which is the normal substrate for 21-hydroxylase.

Most of the affected neonates have random concentrations greater than 3500 ng/dL (105 nmol/L). The diagnosis of classic salt-wasting congenital adrenal hyperplasia (SW CAH) is mostly made in neonates (75 percent are salt-losing). Routine neonatal screening is obligatory in many countries and it is performed in 3-5 days after childbirth. It is essential to note that the setting of preterm babies, birth weight below 2500g and/or distressed neonates, may lead to false positive results. Therefore diagnosis of CAH should include ACTH stimulation test, especially in ambiguous cases. During this test, a synthetic adrenocorticotrophic hormone (Synacthen™) at a dose of 250 µg is injected intravenously.

Then serum 17-hydroxyprogesterone concentrations are marked at baseline, 30 and 60 minutes after dosing. The post-stimulation levels of 17-hydroxyprogesterone are increased in classic-salt wasting congenital adrenal hyperplasia (300-1000 ng/ml) while in classic-simple virilizing congenital adrenal hyperplasia those are decreased (100-300 ng/ml).

Other tests used in the diagnosis of CAH include urinary steroid profiling, which allows accurate assessment of steroidogenesis abnormalities, such as mineralocorticoids and glucocorticoids. Complete Blood Count in patients with classic-salt wasting congenital adrenal hyperplasia present with reduced blood levels of aldosterone and 11-deoxycorticosterone, however plasma renin activity (PRA) is elevated. Moreover, patients present with hypernatremia, hypercalcemia and metabolic acidosis.

Last but not least, genetic testing with the assessment for *CYP21A2* mutation may provide a diagnosis in up to 90–95% of patients. Classic simple virilizing congenital adrenal hyperplasia (SV CAH) in boys and girls may be undiagnosed until early childhood when the signs of precocious maturation develop. Mild clinical forms of SV CAH are sometimes undiagnosed until adult age. The test of choice is measuring the serum levels of 17-hydroxyprogesterone (with the normal values equaling < 1-2 ng/ml) [38].

5. 2. Diagnosis of non-classic congenital adrenal hyperplasia

NC-CAH diagnosis is similar to the diagnosis of classic forms of congenital adrenal hyperplasia. Diagnostic criteria involve the determination of serum 17-hydroxyprogesterone, ACTH stimulation test, urinary steroid profiling, genetic testing for CYP21A2 mutations.

The ACTH stimulation test is a test of choice and usually is decisive in the diagnosis of non-classic congenital adrenal hyperplasia. The 17-OHP concentrations following ACTH stimulation that are typical of NC CAH are most commonly in the range of 15–100 ng/ml.

The biochemical findings are less severe in patients with the non-classic form of the disorder in comparison to classic forms of congenital adrenal hyperplasia [38-42].

5. 3. Differential diagnosis

Polycystic ovary syndrome (PCOS) may present similar clinical picture to CAH due to hyperandrogenic symptoms thus it has always should to be considered in differential diagnosis. Adrenal tumours is another condition that may mimic CAH – in this case, imaging studies are sufficient in differentiation between those two entities [38-42].

6. TREATMENT

The management of CAH depends on the age of onset, sex, and the severity of enzyme deficiency. Treatment aims to improve the patient's quality of life by correction of hormone deficiency as well as alleviation of the symptoms of hyperandrogenism. This is done by application of glucocorticoids (this allows to reduce hyperplasia and overproduction of androgens) in association with mineralocorticoids [38].

Glucocorticoid therapy in patients with congenital adrenal hyperplasia is very complicated and thus it has to be planned carefully. The substitutive doses of GCS are sufficient in the management of adrenocortical insufficiency but in the majority of the cases it fails to provide sufficient suppression of ACTH secretion or to prevent hyperandrogenism and therefore doses should be always adjusted upon correlation with the clinical picture and laboratory findings [38].

Combined contraceptive pills are effective in reducing the signs of hyperandrogenism and should be always considered in management planning [43, 44]. Last but not least, treatment of congenital adrenal hyperplasia may involve surgery.

Bilateral adrenalectomy is seldom used a surgical technique that has limited indications. The principal indication is drug-resistant hyperandrogenism, in which case adrenalectomy allows to limit doses of glucocorticoids [38].

7. CONCLUSION

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is a disorder that requires complex treatment and systematic monitoring. The main task in the care of CAH patients is to establish appropriate medication doses, improve sexuality and fertility, provide psychological support and to prevent other diseases, especially those of cardiovascular system.

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