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Congenital Adrenal Hyperplasia (CAH) - Causes, Diagnosis, Symptoms, Treatment

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Introduction and Purpose: Congenital adrenal hyperplasia represents a group of genetic disorders characterized by improper adrenal steroidogenesis, resulting in deficiency or absence of cortisol and/or aldosterone, and varying degrees of disturbances in sexual development. The aim of this study is to raise awareness about the disease, enabling early diagnosis and contributing to reducing neonatal mortality, as the first clinical manifestation of CAH can be the life-threatening salt-wasting syndrome.

State of Knowledge: Congenital adrenal hyperplasia (CAH), also known as congenital adrenal hyperplasia, encompasses a group of inherited disorders affecting the adrenal glands located above the kidneys.
Adrenal glands produce various hormones, including cortisol, aldosterone, and androgens. CAH involves deficiencies in the enzymes necessary for the production of these hormones, leading to hormonal disturbances.
Summary: Congenital adrenal hyperplasia (CAH), also referred to as congenital adrenal hyperplasia (CAH), describes a group of genetic diseases causing defects in adrenal hormone synthesis. CAH results in deficiency or absence of cortisol and/or aldosterone. The most common causes are mutations in the CYP21 gene (21-hydroxylase deficiency), CYP11B2 gene (11β-hydroxylase deficiency), and HSD3B2 gene (3β-hydroxysteroid dehydrogenase deficiency). Enzymatic deficiencies lead to compensatory increases in CRH and ACTH secretion, causing adrenal hyperplasia and excessive androgen synthesis.

Keywords: CAH, Adrenal hyperplasia; CYP enzymes; CYP genes; Congenital adrenal hyperplasia; Enzymes; Hormones; Steroid; Steroidogenesis.

History

The adrenal gland has been pivotal in the advancement of pediatric endocrinology. Luigi De Crecchio, an Italian anatomist in the 19th century, first documented cases of congenital adrenal hyperplasia (CAH). In the early 20th century, scientists isolated several adrenal steroids, categorizing them into glucocorticoids, mineralocorticoids, and androgens. Lawson Wilkins, a trailblazer in pediatric endocrinology, revolutionized adrenal research by developing modern treatments for CAH. In 1957, Alfred Bongiovanni identified defective 21-hydroxylation in CAH, leading to subsequent discoveries of deficiencies in 3β-hydroxysteroid dehydrogenase and 11β-hydroxylase. Between 1962 and 1964, P450 enzymes were identified, initially linked to 21-hydroxylation. Accurate tests for 17-OH-progesterone in newborns and responses to ACTH enabled early diagnosis of CAH in children and their families. From 1984 to 2004, molecular genetics techniques were applied, elucidating the genetic and biochemical basis of these disorders. Pediatric endocrinologists played a crucial role in identifying responsible genes and establishing effective treatment strategies for various forms of congenital adrenal hyperplasia.

Causes

Congenital adrenal hyperplasia (CAH) is a term used to describe a group of genetic diseases that result in defects in adrenal steroidogenesis, leading to deficiency or absence of cortisol and/or aldosterone synthesis. Several genetic mutations leading to enzymatic deficiencies in the cortisol synthesis pathway have been identified. The most common ones are:

- Mutations in the CYP21 gene - 21-hydroxylase deficiency, which accounts for approximately 90% of cases,
- Mutations in the CYP11B2 gene - 11β-hydroxylase deficiency, accounting for about 10% of cases,

- Mutations in the HSD3B2 gene - 3β-hydroxysteroid dehydrogenase deficiency, accounting for about 1% of cases.

The above enzymatic blocks lead to compensatory increases in CRH and ACTH secretion, resulting not only in adrenal growth and hyperplasia but also in excessive androgen synthesis. Interestingly, other rarer mutations can also lead to CAH, resulting in deficiencies not only in cortisol and aldosterone but also in androgens in the adrenal glands and fetal testes:

- Mutation in the STAR gene - leading to lipid adrenal growth,
- Mutation in the CYP11A gene - responsible for cholesterol desmolase deficiency.

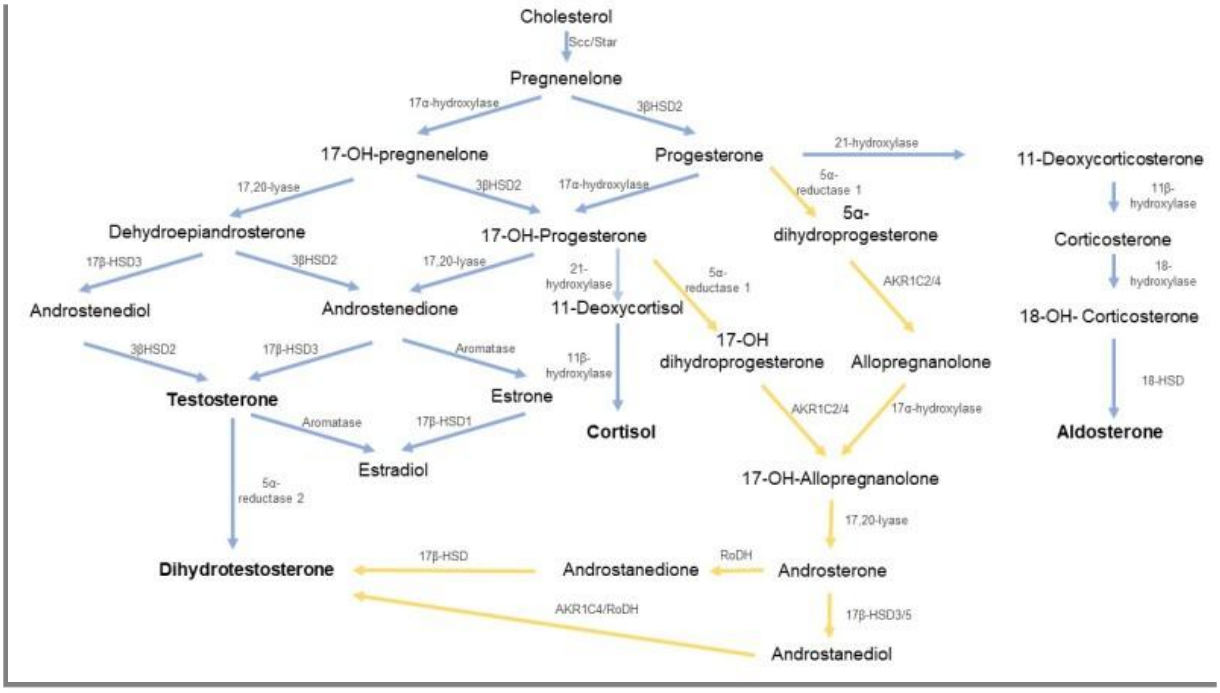
Excess or deficiency of androgens can lead to developmental disorders in fetal development and at birth, providing important diagnostic clues for CAH. This disease is included in the government program for newborn screening in Poland. This enables early diagnosis and treatment, and in many cases prevents death in the neonatal period, as the first clinical manifestation of untreated CAH can be the salt-wasting syndrome, posing a direct threat to the health and/or life of the child.[2,3,4.5]

Classical Form

To illustrate the essence of the issue further in this paper, the disease will be described using the example of the classical form of the most common enzymatic deficiency, which is 21-hydroxylase deficiency. As mentioned earlier, there are several forms of this disease:

- Classical salt-wasting form: Complete absence of the enzyme leads to deficiency of both cortisol and aldosterone.
- Classical simple virilizing form: Partial enzyme activity (about 1-2% of normal) results in deficiency of cortisol only, with aldosterone production preserved.
- Non-classical form: Enzyme activity is preserved at 20-50%, and clinical course and symptoms vary widely.

Due to the congenital enzymatic block at the level of 21-hydroxylase, there is inadequate synthesis of cortisol, and in the salt-wasting form, also aldosterone. This leads to compensatory increase in the secretion of CRH (corticotropin-releasing hormone) and ADH (antidiuretic hormone), followed by ACTH (adrenocorticotropic hormone). Excess ACTH stimulates the adrenal cortex cells to grow and proliferate. Another consequence is the accumulation of precursor molecules before the enzymatic block and excessive synthesis of adrenal androgens. [6,7]



Symptoms

Children with congenital adrenal hyperplasia (CAH) may present symptoms of hypocortisolism, hypoaldosteronism, and hyperandrogenism. In cases where residual enzyme activity is present, symptoms of the disease may not manifest at birth but can appear during periods of increased demand for cortisol, such as infections, stress, or increased physical exertion.

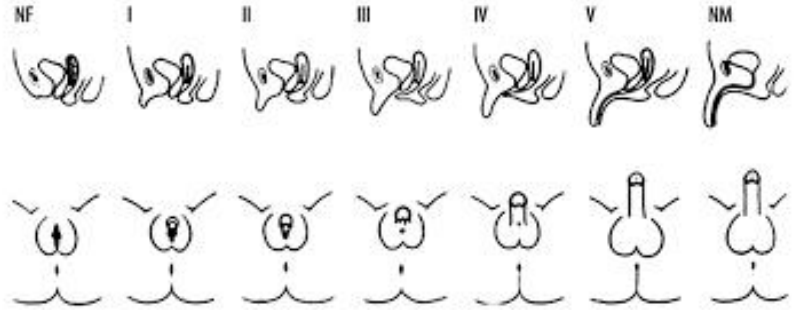
In most patients, inadequate aldosterone synthesis is observed due to complete lack of 21-hydroxylase activity. This condition, along with cortisol deficiency, leads to salt-wasting syndrome. Symptoms of this syndrome can manifest suddenly with deterioration of the general condition, vomiting, dehydration, metabolic acidosis, seizures, hypotonia, hypotension, hypoglycemia, fever, shock, or death. The deterioration typically occurs between the 5th and 14th day of life in the absence of replacement therapy. Infants with the classical salt-wasting form of CAH may also exhibit poor weight gain, reluctance to feed, and may have grayish skin tone.

In girls, a leading symptom indicating and often preceding life-threatening conditions is virilization of the external genitalia. In boys, symptoms of excessive androgenization may be less pronounced, leading to discharge from the neonatal unit before the onset of salt-wasting symptoms.

Scientific studies note that as little as 1% of 21-hydroxylase activity is sufficient for adequate aldosterone synthesis, and defects in aldosterone biosynthesis seen in infancy may improve with age.

As mentioned earlier, the predominant symptom in girls with CAH is varying degrees of virilization of the external genitalia, despite normal internal genitalia. This process can range from minor enlargement of the clitoris to the formation of ambiguous or male external genitalia. The degree of virilization can be assessed using the Prader scale. Surgical correction of the genitalia may often be necessary.[2,5,8]

Prader Scale



Degree I: Slight enlargement of the clitoris, without fusion of the labial folds.
Degree II: Enlargement of the clitoris and fusion of the posterior labial fold.
Degree III: Marked enlargement of the clitoris, shared urogenital sinus, almost complete fusion of the labia.
Degree IV: Further pronounced enlargement of the clitoris, urogenital sinus opening at the base of the clitoris, and almost complete fusion of the labia.
Degree V: Clitoris resembling a penis, urethral opening at the tip of the phallus, labia resembling a scrotum, completely fused.

These degrees assess the degree of virilization of the external genitalia in girls with CAH, which is crucial for clinical assessment and planning further treatment, including potential surgical correction.

In boys, excessive androgenization after birth can result in darkening of the scrotum, nipple area, and penis, as well as thickening of the penis. Mildly expressed symptoms may not raise suspicion or could be overlooked. Symptoms of excessive androgen production affecting both sexes, often observed in inadequately treated or non-classical forms of congenital adrenal hyperplasia (CAH), include: excessive body hair growth, premature pubic and axillary hair development, severe and difficult-to-treat acne, accelerated maturation, and reduced final height due to premature closure of growth plates. In women, symptoms similar to polycystic ovary syndrome may appear, along with menstrual irregularities and male-pattern baldness. [2,8,9]

Diagnosis and Treatment

Appropriate treatment restores normal hormonal balance and enables almost normal growth and proper puberty development.

In Poland, screening tests for congenital adrenal hyperplasia (CAH) are conducted on all newborns. This involves measuring 17-hydroxyprogesterone levels from a dried blood spot collected between the 3rd and 5th day of life. The need for CAH screening in newborns is justified by the high mortality caused by adrenal overactivity, especially among male infants who do not exhibit external signs of the disease. Early diagnosis and prompt treatment can prevent this. In healthy newborns, stress-induced elevated levels of 17-hydroxyprogesterone

can pose diagnostic challenges and lead to false-positive results. However, conducting screening tests should not delay diagnostic procedures when CAH is suspected, especially when abnormal development of external genitalia is observed. [8,9]

When congenital adrenal hyperplasia (CAH) is suspected, serum electrolytes, gasometry, glucose levels, 17-hydroxyprogesterone, dehydroepiandrosterone (DHEAS), ACTH, and karyotyping should be performed. Common findings indicative of CAH due to 21-hydroxylase deficiency include hyperkalemia with hyponatremia, metabolic acidosis, hypoglycemia, elevated levels of 17-hydroxyprogesterone, DHEAS, ACTH, and decreased aldosterone in cases with salt-wasting. If a screening test suggests CAH, in addition to the aforementioned tests, a complete steroid profile from a 24-hour urine collection should be conducted in uncertain cases. Genetic testing should confirm the diagnosis in ambiguous cases.

Currently, prenatal diagnosis through molecular diagnostics allows early intervention, particularly valuable in families with a positive history of CAH. Initiating treatment during the prenatal period, ideally before the 9th week of pregnancy, can prevent virilization of external genitalia. Dexamethasone supplementation effectively suppresses adrenal androgen production and prevents virilization. Dexamethasone is preferred because it minimally binds to cortisol-binding globulin (CBG) in maternal blood and avoids inactivation by placental 11-dehydrogenase, unlike hydrocortisone. However, this approach entails unnecessary treatment in some cases, given CAH's autosomal recessive nature and 25% risk in offspring with a positive family history.

Treatment of CAH currently involves glucocorticoid and mineralocorticoid replacement therapy in cases of salt-wasting syndrome. In acute adrenal insufficiency, electrolyte and glucose levels should be assessed before glucocorticoid administration. A 100 mg/m2 intravenous bolus of hydrocortisone followed by 50-100 mg/m2/day divided into 4 doses is recommended. Simultaneously, correcting hyponatremic dehydration and glucose deficit with 1:1 saline-glucose solution or 0.9% NaCl without potassium supplementation is crucial. Initial fluid bolus should be 20 ml/kg in the first hour, adjusted subsequently based on needs.

For non-crisis CAH, hydrocortisone is used at a replacement dose of 10-15 mg/m2/day orally in 3 divided doses, with fludrocortisone for salt-wasting syndrome at 0.05-0.15 mg/m2/day orally. Additional sodium chloride supplementation (1-3 g/24 h) may be necessary in the first year of life. Chronic glucocorticoid replacement therapy at these doses may be insufficient during stressful events such as infections, trauma, surgery, or general anesthesia, necessitating a threefold increase in oral hydrocortisone for at least 1-2 days to prevent adrenal crisis. During puberty, increased cortisol metabolism requires dosage adjustments based on symptoms and follow-up results, often transitioning to longer-acting glucocorticoids like prednisone or prednisolone post-puberty.

Patient awareness and recognition of symptoms are crucial for effective treatment. Patients and parents should be educated about medication action, adrenal insufficiency symptoms, and the consequences of non-compliance. Proactive dose adjustments during predictable stressors or increased physical activity help prevent adrenal crises.

Effective treatment not only mitigates adrenal insufficiency symptoms but also alleviates hyperandrogenism. Glucocorticoid replacement therapy suppresses excessive CRH and ACTH production, thereby reducing adrenal cortex androgen secretion. [8,9,10]

As mentioned earlier, proper therapy can ensure normal growth and development of the child. However, managing congenital adrenal hyperplasia (CAH) poses challenges, particularly in selecting the appropriate medication dosages. Treatment should aim to eliminate symptoms of hyperandrogenism without inducing clinical or biochemical signs of adrenal insufficiency or overactivity. Clinical assessment is crucial here, as hormone normalization-focused therapy alone may lead to overly high hydrocortisone doses, resulting in numerous complications of hypercortisolism, such as:

- Central obesity with characteristic trunk and neck fat accumulation – "buffalo hump", despite relatively slender limbs
- Rounded, "moon-shaped", often flushed face – plethora
- Red, wide stretch marks on the abdomen, hips, breasts, thighs, around the armpits, and elbows
- Easy bruising and spontaneous skin bruising
- Hypertension
- Muscle weakness and poor exercise tolerance due to muscle wasting in limbs and trunk
- Increased thirst and polyuria as signs of diabetes
- Excessive appetite
- Headaches and dizziness
- Slow-healing skin ulcers
- Emotional instability, depression tendencies, psychotic states, sometimes euphoric, suicidal tendencies, insomnia
- Bone pain as a result of pathological fractures, especially in advanced osteoporosis of the pubic bones, femurs, vertebral bodies, and ribs
- Frequent infections, severe opportunistic infections such as fungal infections
- In men – impotence, decreased libido; in women – scanty menstruation, secondary amenorrhea, anovulation, fertility problems, hirsutism
- Symptoms of secondary hypothyroidism due to inhibition of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH)
- Symptoms of peptic ulcer disease, particularly in individuals taking high doses of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Symptoms of ischemic heart disease due to dyslipidemia and hypertension

If a patient exhibits one or more of these symptoms, a re-evaluation of treatment and adjustment of hydrocortisone doses are necessary. [8,9]

Prognosis

With appropriate treatment, individuals with CAH can lead healthy, normal lives. Regular medical care and monitoring are crucial for managing symptoms and preventing complications.

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