Congenital Adrenal Hyperplasia (CAH; Adrogenital Syndrome) — Symptoms and Treatment

See online here

The gender of the individual coming into being is already fixed on a chromosomal level during the fertilization of the ovum. Gender differentiation occurs during embryogenesis. Disturbances in sexual differentiation can arise due to chromosome anomalies, gene mutations and exogenous or endogenous influences, which are often observed during puberty and cause patients to consult a doctor.

Definition

Congenital adrenal hyperplasia (CAH) describes a group of disorders that comprise of autosomal recessive disorders that each involve a deficiency of an enzyme used in cortisol and/or aldosterone synthesis.

These include 21-hydroxylase, 3β-hydroxysteroid-dehydrogenase, and 11β-hydroxylase deficiencies.

CAH involves a genetically conditioned defect of the enzymes regulating the synthesis of steroid hormones in the adrenal cortex. The result of these enzyme defects is the

increased formation of male sexual hormones (androgens) with virilization of the outer female genitals.

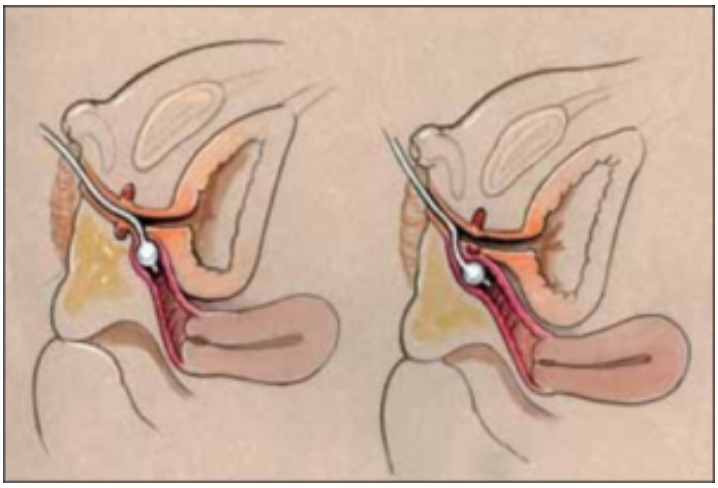

Image: Feminizing genital reconstruction in congenital adrenal hyperplasia.
By: Leslie JA, Cain MP, Rink RC. License: CC BY 2.0

Epidemiology

CAH is the most frequent cause of pseudohermaphroditism in women (chromosomal and gonadal female, physically male).

This autosomal recessive disease occurs with a probability of 1:5000 to 1:15000. A 21-hydroxylase deficiency is the most common form of CAH, representing over 90% of the cases.

Congenital adrenal hypoplasia—North African predisposition:

- More likely to have CAH due to 11β hydroxylase deficiency (2nd MCC of CAH – accounting for 5–8%)
- Occurs in 1 in 100,000 live births in the general population and is more common in some ethnic groups particularly Moroccan Jews

Classification

Generally, every enzyme in the chain of synthesis of the steroid hormones can be affected by a defect. Depending on the affected enzyme, the clinical appearance can vary. **Most frequently affected by a defect are the enzymes:**

- 21-hydroxylase
- 3β-hydroxysteroid-dehydrogenase
- 11β-hydroxylase

The damage to an enzyme can be complete or incomplete which causes differently pronounced pathologies to occur (see below).

21-hydroxylase Deficiency

As the 21-hydroxylase defect is the most common cause of congenital adrenal hyperplasia, with a 95% occurrence rate, the rest of the article will focus on this defect. 21-hydroxylase is a cytochrome p450 enzyme encoded by *CYP21* on chromosome 6p21

within the HLA region. The phenotype strongly correlates with the genotype and reflects residual activity if there is a milder mutation.

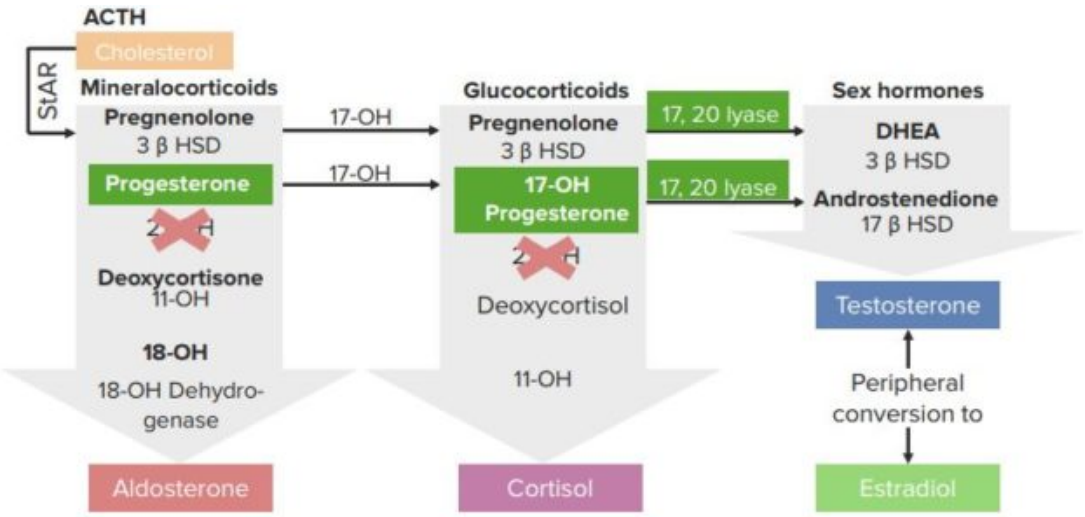

Image: 21-hydroxylase deficiency. By: Lecturio

Etiology

The disease results from genetic mutations and 2 copies of the abnormal genes are required for the expression of the disease as a deficiency in the enzymes involved in adrenal hormone synthesis. The *CYP21A* gene encodes for 21-hydroxylase deficiency.

Pathophysiology

Due to the defect in 21-hydroxylase, cortisol is not produced or is only produced to some extent. Thus, the disease may vary in phenotypic presentation depending on the amount of secreted hormone. The deficiency triggers an increased release of ACTH from the pituitary due to a lack of negative feedback in the superior hormone centers. ACTH stimulates the adrenal cortex, leading to hyperplasia.

The result is an increased production of androgens and an accumulation of intermediate products that are used for androgenic synthesis.

Symptoms and Pathology

This section explains the impact of the disease in female patients.

The patients have the karyotype 46 XX and the female inner genitals are normally formed. The outer genitals, however, experience masculinization (virilization), which can be pronounced to different extents, depending on the excess synthesis of androgens. The forms of masculinization range from hypertrophy of the clitoris alone to a merging of the labioscrotal folds and formation of the male urethra.

The time of manifestation of the disease can vary—from the fetal period, through childhood, as well as during or after puberty.

In the case of a classic 21-hydroxylase defect, the virilization of female fetuses has already occurred prenatally. Thus, the child is born with masculinized outer genitals with

varying presentations at birth.

If left untreated, the growth of pubic and underarm hair already begins at the age of 2 years. Additionally, children are at first larger than others of the same age, but when they reach adolescence or adulthood, growth stops because of early closure of the epiphyseal plates. In addition to the growth of male body hair (hirsutism), a change in voice can also occur. Patients do not reach female puberty and therefore experience amenorrhea and infertility.

The non-classic 21-hydroxylase defect (late-onset CAH) manifests only in the course of time, which means that the affected girls appear normal at birth. The onset of the disease during puberty is characterized by a mild course of virilization (acne, hirsutism, and seborrhea are possible). Additionally, menstruation disorders with prolonged cycles or amenorrhea can occur.

In the cryptic form of 21-hydroxylase defect, the androgenization is very mildly pronounced or entirely absent.

In some cases, the synthesis of aldosterone can also be restricted, which results in a salt-wasting syndrome with exsiccosis, hyponatremia, hypokalemia, and acidosis. Affected babies are apathetic, throw up frequently and need immediate therapy as they are in vital danger.

Diagnostics and Differential Diagnosis

Chromosomal sex can be determined by chromosomal analysis. Different intermediate levels of cortisol synthesis, which become noticeable depending on the faulty enzyme, can be determined endocrinologically. Furthermore, the metabolites produced in the preliminary stages of cortisol synthesis can be found in the urine (e.g. pregnanetriol).

To differentiate the type of 21-hydroxylase defect, the ACTH-stimulation test can be performed. Blood is drawn to determine the 17-hydroxyprogesterone and cortisol levels, then ACTH (250 mg IV) is administered. After 1 hour, the levels of 17-hydroxyprogesterone and cortisol are determined again. If the difference between the first and the second value of 17-hydroxyprogesterone does not exceed 2.5 ng/mL, it is a normal reaction. An increased level of cortisol shows adrenal cortex hyperplasia.

Therapy

CAH should be treated as soon as possible to prevent virilization of the patient and to achieve normalized ovarian function. Affected individuals must take glucocorticoids (e.g. hydrocortisone or dexamethasone) for life. Thus, ACTH production and the formation of androgens is reduced.

The therapy should be adjusted individually as Cushing syndrome and growth inhibition can occur. If the therapy is sufficient, normal female development is achieved and the infertility of the patients can be reversed, making pregnancy possible. When healthy descendants are born, they are carriers of CAH.

Note: Cushing syndrome develops due to glucocorticoid overdose.

If there is a salt-wasting syndrome, additional mineralocorticoids (e.g. fludrocortisone) are required and electrolyte disorders have to be treated.

Prevention

CAH is an autosomal recessive disorder. This means that if a mother has a child with CAH, there is a 25% probability that another pregnancy will also result in a child with CAH. Taking dexamethasone (1—1.5 mg/d) during the pregnancy can prevent the virilization of an affected child. The intake of dexamethasone can be stopped when there is proof of a male fetus or the exclusion of CAH at a later point in the pregnancy based on prenatal diagnostics.

Notes