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 on Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is a group of disorders that comprises of autosomal recessive disorders each of which involves a deficiency of an enzyme used in cortisol and/or aldosterone synthesis.

They include 21-hydroxylase deficiency, 3β-hydroxysteroid-dehydrogenase, and 11β-hydroxylase.

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 of Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia, or CAH, is the most frequent cause of Pseudohermaphroditism femininus (chromosomal and gonadal female, habitus male).

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

CAH 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 of Congenital Adrenal Hyperplasia

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-OH Deficiency**

As the 21-hydroxylase defect is the most common cause of congenital adrenal hyperplasia, with a presence in 95 % of the cases, the rest of the article will focus on this defect. 21 hydroxylase is a cytochrome p450 enzyme encode by CYP21 on chromosome
6p21 within the HLA region. Phenotype strongly correlates with genotype and reflects residual activity if there is a milder mutation.

**Etiology of Congenital Adrenal Hyperplasia**

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

**Pathophysiology of Congenital Adrenal Hyperplasia**

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. The ACTH stimulates the adrenal cortex, and it results in a hyperplasia.

The result is an increased production of androgens and an accumulation of intermediate products which are, in turn, used for the androgenic synthesis.

**Symptoms and Pathology of Congenital Adrenal Hyperplasia**

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

The patients have the karyotype 46, XX and female inner genitals which 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 reach from sole hypertrophy of the clitoris to a merging of the labioscrotal folds and formation of a 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 classic 21-hydroxylase defect, the virilization of female fetuses has already occurred prenatally. Thus the child is born with masculinized outer genitals, pronounced to different extents at birth.

If left untreated, the growth of pubic and underarm hair already begins at the age of two. Additionally, children are at first larger than others of the same age, but when they reach adolescence or adulthood, growth stops because of an early closure of the epiphyseal plates. In addition to growth of male body hair (hirsutism), a change in voice can also occur. Patients do not reach female puberty and therefore suffer from 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 are still unobtrusive 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 just a little pronounced or is 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 an immediate therapy as they are in vital danger.

Diagnostics and Differential Diagnostics of Congenital Adrenal Hyperplasia

The chromosomal gender 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 21-hydroxylase defect, the ACTH-stimulation test can be performed. Blood is drawn to determine the 17-OH-progesterone and cortisol levels, then ACTH (250 mg i.v.) is administered. After one hour, the levels 17-OH-progesterone and cortisol are determined again. If the difference between the first and the second value of 17-OH-progesterone does not exceed 2,5 ng/ml, it is a normal reaction. An increased level of cortisol shows an adrenal cortex hyperplasia.

Therapy of Congenital Adrenal Hyperplasia

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

The therapy should be adjusted individually as a Cushing syndrome and a growth inhibition can occur. If the therapy is sufficient, a normal female development is achieved and the infertility of the patients can be reversed, thus making pregnancy possible. When healthy descendants are born, they are carriers of CAH.
Note: Cushing syndrome has developed the case of an overdose on glucocortides!

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

**Prevention of Congenital Adrenal Hyperplasia**

CAH is an autosomal disorder inherited recessively. This means that if a mother has born a child with CAH, there is a 25% probability that another pregnancy will also result in a child who has CAH. By means of taking dexamethasone (1—1.5 mg/d) during the pregnancy, the virilization of an affected child can be avoided. The intake of dexamethasone can be stopped when there is proof for male gender or an exclusion of CAH at a later point in the pregnancy by prenatal diagnostics.

**References**


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