

# Classic congenital adrenal hyperplasia

Congenital adrenal hyperplasia is caused by hereditary enzyme defects in the adrenal cortex. The classic form results in reduced production of cortisol and aldosterone accompanied by increased production of adrenocortical androgens. This causes virilisation in girls and adrenocortical insufficiency and precocious puberty in both sexes. In this article we describe the genetics, clinical picture, diagnostics and treatment.

Congenital adrenal hyperplasia is caused by enzyme failure in the steroid biosynthesis of the adrenal cortex. In more than 95% of patients, mutations in the *CYP21A2* gene result in reduced activity of the 21-hydroxylase enzyme. Failure of this enzyme causes reduced production of aldosterone and cortisol, leading to increased secretion of the adrenocorticotrophic hormone (ACTH) from the hypophysis. This stimulates biosynthesis of the adrenocortical androgens, which are independent of 21-hydroxylase, with an accumulation of 17-hydroxyprogesterone, androstenedione and testosterone (Fig. 1). Other forms of congenital adrenal hyperplasia due to other specific defective genes with different phenotypes occur more rarely.

Congenital adrenal hyperplasia is the most frequent cause of gender ambiguity at birth, because girls are virilised during foetal life (1). Non-classical congenital adrenal hyperplasia is due to mild mutations that do not result in cortisol or aldosterone deficiency, but hyperandrogenism in adult women. This article concerns the classical form.

The article is based on the authors' own research and experience, and recent international literature.

## Epidemiology and genetics

Based on neonatal screening, the global prevalence of classical congenital adrenal hyperplasia is approximately 1/15 000, but there is wide variation between population groups (1). In Sweden, where neonatal screening was introduced in 1986, the prevalence is 1/8 900 (2). In Norway the prevalence is estimated to be 1/16 000, or around four new children per year (3).

The disease is recessively inherited, and genotype is highly correlated with clinical phenotype.

## Clinical presentation

Congenital adrenal hyperplasia is categorised into classical and non-classical forms (Table 1) (4, 5), of which the classical form includes salt-wasting and non-salt-wasting forms. In the salt-wasting form, enzyme activity is extremely low, which results in

deficiency of both aldosterone and cortisol. The salt-wasting form has its onset as an adrenal crisis, with vomiting, dehydration, hypoglycaemia and hypotension as well as pronounced hyperkalaemia and hyponatraemia in the first weeks after birth. In the non-salt-wasting form, a certain level of enzyme function is preserved so that aldosterone production is sufficient to prevent sodium loss, and cortisol deficiency is somewhat reduced.

In both forms, girls are born with virilisation of the external genitalia. This is usually most pronounced in the salt-wasting form of the disease. Characteristic findings are an enlarged clitoris, partial labial fusion and a shared urogenital sinus. The internal genitalia, such as the uterus and ovaries, are normal. Before the introduction of neonatal screening, most girls with congenital adrenal hyperplasia were diagnosed in the neonatal period, but delayed diagnosis and misinterpretation of gender have occurred.

If untreated, girls will undergo a voice change, be significantly virilised and have growth retardation. Prenatal androgen exposure in girls can lead to masculine gender role behaviour (6). Boys go through early puberty and may be fully grown at only seven years of age.

## Neonatal screening and diagnostics

Routine ultrasound examination in pregnancy cannot detect the condition, but since 2012, congenital adrenal hyperplasia has been included in neonatal screening in Norway. The test is performed by measuring 17-hydroxyprogesterone in blood on filter paper no earlier than 48 hours after the birth. The aim is to prevent neonatal death, determine the sex and prevent precocious puberty.

Since neonatal screening was introduced in Sweden, more children have been diagnosed with the salt-wasting form of the condition, and more have survived (2).

## Treatment

### General treatment and follow-up

Follow-up of the patients is focused on hormonal as well as psychological factors at all life stages. In newborns, key issues relate to

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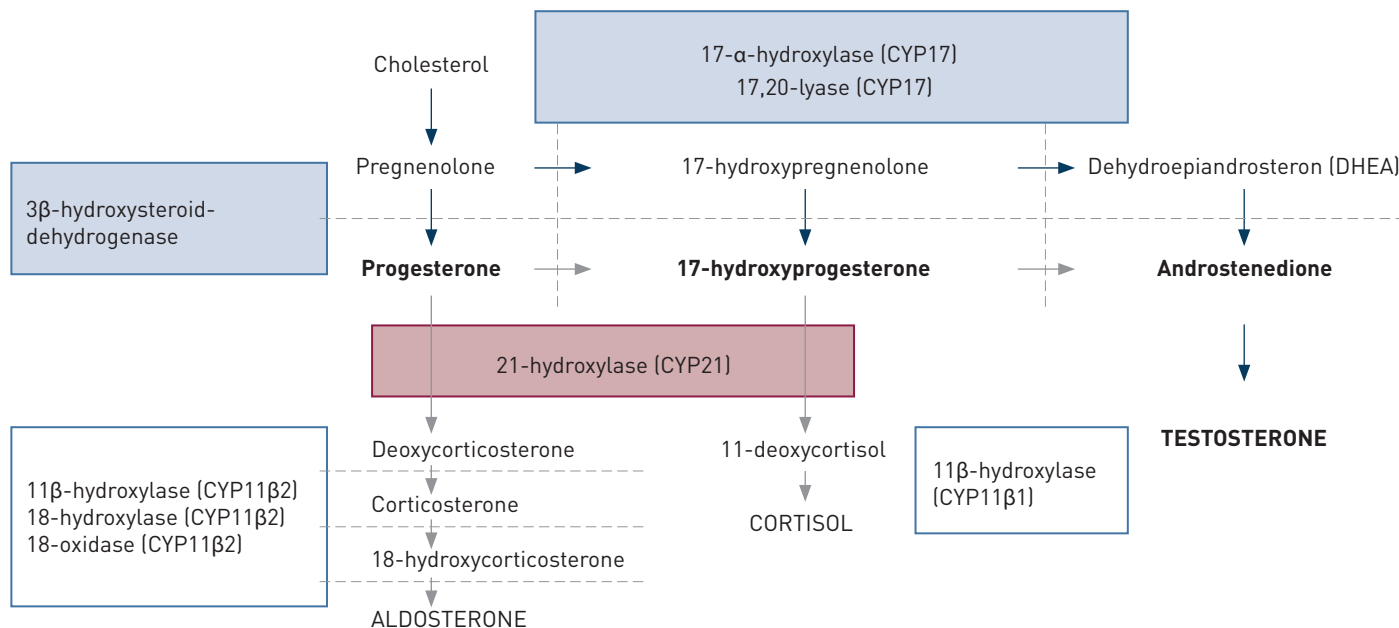
## MAIN MESSAGE

**Congenital adrenal hyperplasia is a rare hereditary disorder with impaired enzyme activity in the adrenal cortex**

**The illness results in reduced cortisol and aldosterone production and virilisation in girls**

**The treatment consists of a balance between substitution and suppression of glucocorticoids and mineralocorticoids. Overtreatment with glucocorticoids should be avoided**

**Patients should possess a Norwegian steroid card and receive training in intramuscular self-injection of hydrocortisone (Solu-Cortef) in crisis situations**



**Figure 1** Congenital adrenal hyperplasia is due to hereditary enzyme defects in the adrenal cortex. The red box shows the 21-hydroxylase enzyme, and CYP21A2 is the mutated gene. The blue boxes show rare enzyme defects with corresponding CYP gene

diagnostics, sex determination and avoiding adrenal crises.

In infancy there is a risk of urinary tract infection in girls, and genital surgery may be needed. Children are closely followed-up in paediatric units with particular expertise in steroid replacement therapy. Girls with congenital adrenal hyperplasia and their families should be offered follow-up through to adulthood in a multidisciplinary team consisting of a paediatrician, paediatric surgeon, psychologist/psychiatrist and gynaecologist.

Adults with congenital adrenal hyperplasia should be monitored by an endocrinologist. The purpose of drug treatment is to *replace* the vital hormones aldosterone and cortisol as well as to *suppress* ACTH production, so that the levels of adrenocortical androgens are reduced. Optimal treatment will prevent ACTH-stimulated growth of the adrenal glands and development of benign tumours.

Hyperandrogenism in women results in irregular menstruation and infertility, which can be improved with the correct corticosteroid treatment. Despite the problems associated with virilisation, only 40% of Norwegian women with congenital adrenal hyperplasia have attended for a gynaecological examination in adulthood (3).

**Glucocorticoids**

Particularly challenging in the treatment of these patients is the balance between replacement and suppression. The dosage required for suppression must frequently be higher than the necessary replacement dos-

age. This entails a heightened risk of adverse effects such as overweight, metabolic syndrome, growth retardation and osteopenia. Treatment is monitored by measuring speed of growth and bone age in children and measuring 17-hydroxyprogesterone level. The value should be just above the reference range to avoid overtreatment.

The natural glucocorticoids, cortisone and hydrocortisone (cortisol) are short-acting and therefore do not provide ACTH suppression in the early hours. In order to balance this and ensure adequate suppression throughout the 24-hour period, synthetic glucocorticoids

such as prednisolone and dexamethasone can be administered in the evening, but this also increases the risk of overdose and is not recommended for growing children. Unfortunately, this treatment does not recreate the normal 24-hour profile of cortisol, and drugs with modified-release hydrocortisone are being developed (7). Continuous subcutaneous hydrocortisone infusion can be beneficial for some patients (8).

Separate international guidelines exist for glucocorticoid therapy in children. These recommend hydrocortisone, which presents the least risk of growth retardation (9).

**Table 1** Distribution of 21-hydroxylase deficiency conditions (4, 5) (modified). ↓ = reduced ↓↓ = no production

Characteristic	Classical type		Non-classical type
	Salt-wasting	Non-salt-wasting	
Age at time of diagnosis <sup>1</sup>	Neonatal period	Neonatal period (women) or childhood (men)	From infancy to adulthood
Virilisation/hirsutism	Moderate to pronounced	Moderate to pronounced	None to slight or moderate, may undergo precocious puberty
Percentage enzyme activity	0	1–10%	30–75%
Aldosterone	↓↓	↓ Normal	Normal
Cortisol	↓↓	↓	Normal

<sup>1</sup> In countries with neonatal screening, such as Norway, classical congenital adrenal hyperplasia is diagnosed in the neonatal period

There are no international guidelines for adults (4). We recommend cortisone acetate (cortisone tablets) 25–37.5 mg, distributed in 2–3 doses, possibly with the addition of prednisolone 2.5 mg in the evening.

#### Essential training

It is essential that patients understand that they must increase the dosages in case of acute illness – to avoid adrenal crises. *All patients* should have received a Norwegian steroid card and must be trained in intramuscular self-injection of hydrocortisone (Solu-Cortef) in crisis situations (10).

#### Mineralocorticoids

Fludrocortisone (Florinef) is the only available mineralocorticoid and is recommended for all children with congenital adrenal hyperplasia (9). After final adult height is reached, many with the non-salt-wasting form can manage without fludrocortisone, but it may be beneficial to continue with the drug because it may reduce the need for glucocorticoids. In Norway adult patients use less fludrocortisone than in other countries (3). The dose varies from 50 µg to 200 µg daily, irrespective of body size, administered in a single dose.

A craving for salt and orthostatic drop in blood pressure indicates underdosage. The dosage is assessed based on blood pressure, electrolytes and plasma renin activity, which should be in the upper part of the normal range or slightly over. It is essential to inform patients about the importance of sufficient salt intake.

#### Psychosocial follow-up

Parents who have a child whose gender is uncertain will as a rule find this to be very difficult. A national treatment service has therefore been established with an interdisciplinary team at Oslo University Hospital and Haukeland University Hospital, which will be responsible for initial assessment and treatment for these children.

Adult women with congenital adrenal hyperplasia may experience higher psychological stress, for example because of previous genital surgery, masculine gender role behaviour, questions of sexuality, amenorrhoea, fertility and identity, and they should be offered psychological follow-up.

### Clinical course

#### Height

Adults with congenital adrenal hyperplasia are shorter in stature than the normal population, because of androgen-driven precocious puberty as well as growth retardation resulting from overdosage of glucocorticoids. Final median height for Norwegian women and men is 6.3 cm and 11.2 cm below the median height for the general population, respectively (11).

#### Body composition, bone density and fractures

Glucocorticoids increase the fat mass and reduce muscle mass and bone density, while androgens have the opposite effect. Many studies report high body mass index in children, adolescents and adults with congenital adrenal hyperplasia (12, 13). We found that these patients have a higher fat mass than the general population, especially in the case of younger women (11). Studies of adults have also shown that these patients have reduced bone density (11, 12).

#### Cardiovascular and other diseases

In a recent Swedish registry study, the prevalence of cardiovascular and metabolic diseases in patients with congenital adrenal hyperplasia was almost four times higher than in the general population (OR 3.9; 95% CI 3.1–5.0). There was also an increased prevalence of hypertension, atrial fibrillation, venous thromboembolism, obesity, type 2 diabetes and obstructive sleep apnoea (14).

#### Adrenal and testicular tumours

The patients are vulnerable to developing adrenal tumours, especially myelolipomas (15). Myelolipomas are benign, inhomogenous, fatty tumours that rarely require surgical treatment. Congenital adrenal hyperplasia is a differential diagnosis in cases of incidental findings of adrenal tumours and findings of adrenal hyperplasia. Multiple older Norwegian men have received a diagnosis of classical adrenal hyperplasia following incidental findings of enlarged adrenal glands with an abdominal CT scan.

Men with congenital adrenal hyperplasia have a higher risk of testicular adrenal rest tumours. These are benign testicular tumours emanating from ectopic adrenal tissue which grows during long-term ACTH stimulation (16). In a Norwegian study that included 23 men with congenital adrenal hyperplasia, altogether 57% of those with the salt-wasting form, but none with the non-salt-wasting form, had these types of tumours (15).

If these adrenal rest tumours become large, they may lead to obstructive azoospermia and irreversible damage to the testicular parenchyma, with fibrosis, gonad dysfunction and infertility (16). Location of tumours close to the rete testis renders them difficult to detect during clinical examination, and regular ultrasound examination is proposed as routine (4, 9).

#### Fertility

Low rates of pregnancy are reported in women with congenital adrenal hyperplasia, and this applies particularly to the salt-wasting form of the disease (3). Many factors may contribute to this, such as virilisation of

the external genitalia, oligo- or amenorrhoea and anovulation. In women there is also a higher prevalence of homosexual orientation and single status (17).

Fertility in men with congenital adrenal hyperplasia may vary from normal to significantly lowered, and it is known that testicular adrenal rest tumours may cause reduced fertility (16).

#### Health-related quality of life

Studies of health-related quality of life reveal different results, but the largest studies, from Norway, the United Kingdom and Germany, show a significantly lower quality of life than for the general population (3, 12, 18).

### Conclusion

Congenital adrenal hyperplasia is a disease that entails several problem areas requiring specialised, multidisciplinary follow-up. Hormone treatment constitutes a difficult balance between under- and overdosage.

The patients report reduced quality of life, and the condition also entails numerous psychological challenges. GPs and other doctors who treat adult patients with congenital adrenal hyperplasia should ensure that these patients receive follow-up from a specialist.

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