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How to manage puberty and prevent fertility disorders in men with CAH?

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INFO ARTICLE

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ABSTRACT

Gonadal dysfunction is an adverse outcome in patients with congenital adrenal hyperplasia (CAH), which may become apparent already during puberty. In males, gonadal dysfunction can be caused by primary gonadal failure due to testicular adrenal rest tumours (TART), and by secondary gonadal failure due to poor hormonal control. Yearly evaluation for TART using ultrasonography is recommended from the start of puberty or even earlier when poor hormonal control is present. We recommend yearly evaluation of gonadal function by measuring LH, FSH, testosterone, and inhibin B. When TART is present, cryopreservation of semen should be considered as soon as possible.

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by mutations in one of the genes coding enzymes that are involved in the adrenal steroidogenesis [1–4]. The most common cause (more than 95% cases) is due to 21-hydroxylase deficiency (21OHD). This enzymatic defect leads to a decreased production of cortisol with consequently lack of the negative feedback to the ACTH production in the pituitary gland. Chronically elevated ACTH levels lead to chronic stimulation of the adrenal cortex with consequently accumulation of adrenal precursor steroids before the enzymatic block i.e. 17 hydroxyprogesterone (17OHP) and progesterone (P). These elevated precursors are shifted into the non-affected adrenal androgen pathway leading to strongly elevated production of adrenal androgens. Therefore, typical biochemical characteristics of 21OHD are a lack of cortisol and in the most severe cases also of aldosterone and increased concentrations of adrenal androgens and precursor steroids. The lack of cortisol and the increased production of androgens are responsible for the typical clinical symptoms in CAH patients: Females with classic CAH are generally virilized, the lack of aldosterone leads to salt wasting and salt wasting crisis. All patients are at risk to develop life threatening Addisonian crisis.

Therefore, CAH treatment has two aims: 1. to substitute the deficient steroid hormones and prevent the occurrence of adrenal and salt wasting crises, and 2. to restore the negative feedback mechanism towards hypothalamic CRH secretion and pituitary ACTH secretion to diminish adrenal androgen overproduction. Traditionally, glucocorticoids are used to substitute for cortisol and to restore the negative feedback on the pituitary gland. Unfortunately supraphysiological doses are often necessary to reach this goal with the risk of unfavorable effects of cortisol overreplacement such as weight gain, cushingoid features and metabolic syndrome. The balance between over and undertreatment can be challenging in individual patients, especially during puberty hormonal control is often far from optimal mainly due to lack of compliance. Poor hormonal control is related to gonadal dysfunction already in adolescents.

Gonadal dysfunction is one of the most important long term complications in male and female patients with classic CAH and the most common cause of infertility. In males gonadal function can be impaired due to primary gonadal failure mostly caused by testicular adrenal rest tumors (TART) and/or secondary gonadal failure caused by suppression of the hypothalamic pituitary gonadal axis. In both cases the primary cause is poor hormonal control with subsequent elevated ACTH concentrations and elevated adrenal androgens concentrations. Signs of gonadal dysfunction can already be present during puberty and therefore also pediatric endocrinologist should monitor carefully pubertal development and gonadal function in both males and females.

Testicular adrenal rest tumours (TART)

Typical testicular tumours in male patients with CAH were already described in 1940. Histologically, these benign tumours

Abbreviations: CAH, Congenital adrenal hyperplasia
TART, Testicular adrenal rest tumor
21OHD, 21-hydroxylase deficiency
17OHP, 17 hydroxyprogesterone
P, Progesterone.

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resemble adrenocortical cells and they were originally thought to arise from aberrant adrenal cells in the testes that are stimulated by elevated ACTH. Therefore, they were named testicular adrenal rest tumours (TART). TART are often present bilaterally (> 80% of the cases) and have a typical central location within the rete testes. The reported prevalence varies between 0-94% and depends mainly on the method of detection, age of the patient and severity of CAH. TART lesions below 2 cm are generally not detectable by palpation due to the central location within the testes. Therefore, we recommend using imaging techniques such as ultrasound or MRI. TART can already be detected during childhood with a clear increase in prevalence during puberty and adulthood. TART is mainly present in males with classic forms of CAH (salt wasting, simple virilising).

Due to the central location in the testes TART can lead to mechanical obstruction of the seminiferous tubules with consequently obstructive azoospermia. This longstanding obstruction can result in irreversible damage to the surrounding testicular tissue.

It is thought that elevated ACTH levels play an important role in the pathogenesis of TART. As TART is most often described in patients with poor hormonal control, intensifying glucocorticoid treatment is the first choice of treatment. Several case reports described shrinkage of the tumor after intensifying glucocorticoid therapy and consequently suppression of ACTH. However, medical treatment is not always successful and with higher dosages of glucocorticoids the risk of serious side effects such as hypertension and weight gain may increase. Other treatment options such as mitotane are still experimental. In the presence of TART the possibility of cryopreservation should be discussed with the patient in an early stage.

Secondary gonadal failure in male CAH patients

Especially poorly controlled CAH patients are at risk of developing secondary gonadal failure besides the development of TART. High concentrations of adrenal androgens (androstenedione) are aromatised to estrone which will suppress the hypothalamic-pituitary-gonadal axis, leading to hypogonadotropic hypogonadism and small testes.

In contrast to other forms of secondary hypogonadism, most CAH patients do not report complaints from testosterone deficiency as male CAH patients with poor hormonal control usually have sufficient testosterone from adrenal origin. Therefore, even in patients with apparently normal gonadotropin and testosterone levels, gonadal function can be severely impaired. Inhibin B seems to be a better marker for Sertoli cell function and should be checked regularly. To distinguish testosterone from adrenal and testicular origin, it has been suggested to use the serum androstenedione to testosterone ratio in male CAH patients, as androstenedione is elevated when the androgens are predominantly of adrenal origin. One has to be aware that serum total testosterone can be decreased due to low serum SHBG concentrations, for example in obese patients, or elevated in some conditions such as hepatitis or hyperthyroidism. Therefore, free testosterone should be measured or calculated from total testosterone, SHBG and albumin concentrations.

In the absence of TART, most reports show reversible hypogonadism and improved fertility after initiating or increasing glucocorticoid therapy.

Practical recommendations (adapted from Eur J Endocrinol 2021, 184:R85-R97)

Optimal hormonal control is a key factor for adequate gonadal function in male and female CAH patients, already during adolescence and young adulthood. During puberty an increased clearance of glucocorticoids is observed due to a decreased activity of 11β HSD1 making higher glucocorticoid dosages in this period necessary. However, higher levels of glucocorticoids are also negatively correlated with reduced final height and dosages above 17 mg/m^2/day should be avoided. Frequent monitoring of hormonal control is important to balance over/undertreatment also in different periods over the day.

Yearly evaluation for TART using ultrasonography is recommended from the start of puberty, but only in classic forms of CAH. We recommend yearly evaluation of gonadal function by measuring LH, FSH, (free) testosterone, SHBG and inhibin B levels. Normal levels of gonadotropines and testosterone do not rule out gonadal dysfunction especially in patients with small testis volumes. Consider using the androstenedione to testosterone ratio to differentiate between an adrenal and a testicular origin of the androgens. When TART is present, the patient should be referred to an urologist for evaluation and cryopreservation of semen as soon as possible.

Disclosure of interest

The author declares that he has no competing interest.

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