Congenital adrenal hyperplasia

Helen Simpson

Ieuan Hughes

Abstract

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder of adrenal corticosteroid biosynthesis affecting 1/10,000–15,000 live births. The most common form is 21-hydroxylase deficiency caused by mutations in the *CYP21A2* gene. CAH classically presents at birth with ambiguous genitalia in an affected girl. Salt loss, which can be life-threatening, is the only sign in an affected newborn boy. An adolescent girl with CAH has a syndrome of hirsutism, acne and irregular periods. Treatment aims to replace adequate amounts of glucocorticoid and mineralocorticoid hormones, but avoid adverse effects such as growth suppression in childhood, and obesity and adverse metabolic profile in adult life. Serum 17OH-progesterone and adrenal androgens are increased in CAH because of 21-hydroxylase deficiency and can be useful markers to monitor treatment. Surgery for ambiguous genitalia is usually performed around 12–18 months of age if a reduction in size of the clitoris is needed. However, this can damage nerves and affect later sexual function. Vaginoplasty can be deferred until puberty. The option of prenatal treatment with dexamethasone to prevent virilization of an affected female fetus has lacked diagnostic specificity. Fetal DNA analysis of early maternal serum samples now avoids unnecessary fetal exposure to potent glucocorticoids.

Keywords 17OH-progesterone; adrenal corticosteroid synthesis; ambiguous genitalia; clitoris; genotype; phenotype; prenatal treatment; vaginoplasty

Key points

- CAH is the commonest cause of ambiguous genitalia of the newborn
- 21-hydroxylase deficiency is the commonest form of CAH
- Glucocorticoid treatment is geared to provide sufficient steroid replacement for safety and reducing excess androgens, but not at the expense of side effects
- Modified-release hydrocortisone preparations that aim to replicate the endogenous cortisol dynamics show promising results in clinical trials
- CAH has significant cardiovascular and metabolic morbidity in later adult life
- Reproductive capacity for both females and males with CAH can be improved with optimal medical control and the use of artificial reproductive techniques
- The indications for, and the timing of, genital surgery for females with CAH should be assessed in the context of longer term outcomes
- Prenatal treatment with dexamethasone can now be specifically targeted to the affected female fetus but should only be used in clinical trials committed to assess the long-term effects postnatally

Introduction

Congenital adrenal hyperplasia (CAH) is a life-long autosomal recessive disorder of adrenal corticosteroid biosynthesis. Clinical presentation varies according to severity of corticosteroid enzyme deficiency and patient age. It classically presents at birth with ambiguity of the external genitalia in an affected girl.

Pathophysiology

The adrenal cortex produces glucocorticoids, mineralocorticoids and sex hormones. Cortisol production is dependent on adrenocorticotrophic hormone (ACTH) and controlled via a classic negative-feedback mechanism. Aldosterone production is under the control of the renin–angiotensin system. Cholesterol is the starting point in all corticosteroid-producing endocrine glands, with several enzymatic steps required for cortisol and aldosterone production. Defects in the early steps of corticosteroid biosynthesis, such as deficiencies in steroid acute regulatory protein, 3β-hydroxysteroid dehydrogenase and 17,20-lyase, also affect gonadal corticosteroid production; these rare forms of CAH are not discussed here.

Deficiency of 11β -hydroxylase, the final enzymatic step in cortisol production, accounts for about 5% of cases. This also causes virilization of an affected girl at birth; however, salt retention from the effects of increased 11-deoxycorticosterone, rather than salt wasting, characterizes this form of CAH. Hypertension is usually identified in late childhood or adolescence and can be severe.

Figure 1 shows the pathophysiological consequences of 21-hydroxylase deficiency, the most common enzyme deficiency causing CAH.[1] The accumulation of 17OH-progesterone under the continued ACTH drive, because of underproduction of cortisol, leads to excessive production of adrenal androgens that are converted in the liver to testosterone. A female fetus, exposed to androgens from as early as 8 weeks of gestation, has an enlarged clitoris and fusion of the labioscrotal folds. The degree of virilization can give the appearance of normal male genitalia. However, the absence of palpable testes should prompt further

Helen Simpson *MRCP PhD is a Consultant Endocrinologist at University College Hospital, London, UK. Competing interests: none declared.*

Ieuan Hughes *MD FRCP FRCPCH FMedSci is Emeritus Professor of Paediatrics at the University of Cambridge, UK. Competing interests: none declared.*

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Simpson H, Hughes I, Congenital adrenal hyperplasia, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.05.012

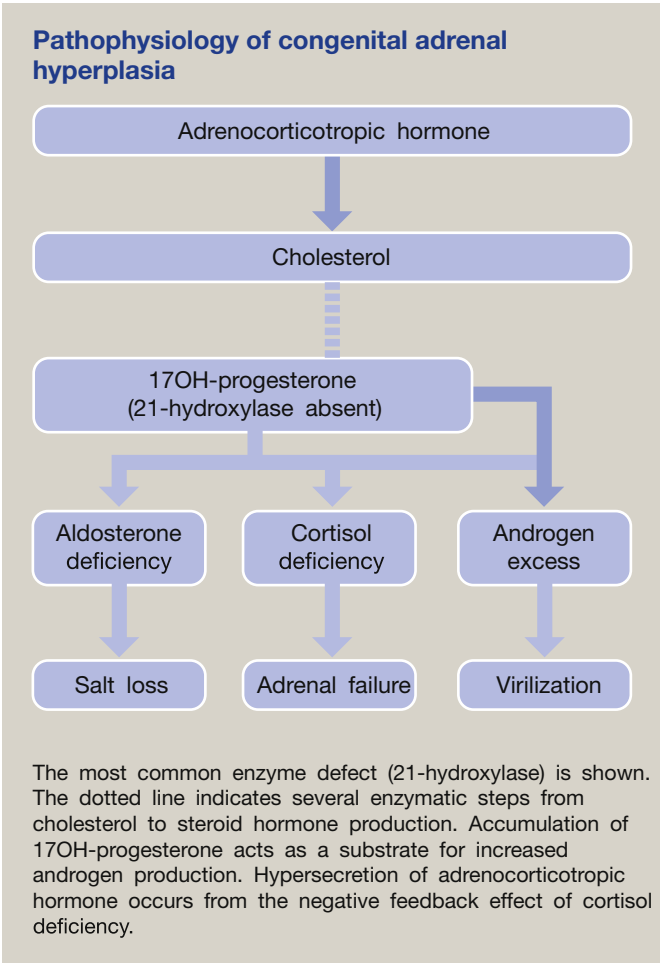

Figure 1

investigation. Affected male infants are not 'supervirilized' at birth, although the scrotal skin can appear hyperpigmented. The 21-hydroxylase enzyme is also required to synthesize aldosterone, so salt loss occurs in most newborns with CAH. This is typically the only clue to the diagnosis in affected male newborns.

The 21-hydroxylase form of CAH is present in >90% of individuals and is caused by mutations in the *CYP21A2* gene, on the short arm of chromosome 6. About 10 different mutations account for the vast majority of cases of 21-hydroxylase deficiency. These include large gene deletions and chimaeric genes resulting from misalignment and unequal crossover during meiosis, which together account for 25–30% of cases of deficiency. About 65–75% of patients are compound heterozygotes for *CYP21A2* mutations.

Epidemiology

CAH has an incidence of 1/10,000–15,000 live births, based on figures from newborn screening programmes in several developed countries. A precise figure is not available in the UK as CAH is not a component of the newborn screening programme. The incidence is about 1/12,000 births on clinical case ascertainment with no sex imbalance, as expected for an autosomal recessive disorder. This is the *raison d'etre* for screening to prevent death from CAH in male infants. Furthermore, the blood spots for newborn screening tests in the UK are not collected until 5–7 days after birth whereby a male infant may have presented with salt wasting before the 17OH-progesterone result becomes available. The mild or late-onset form of CAH has an incidence as high as 1/1000, and occurs in about 6% of women who are hirsute. This form of CAH is not detected by newborn screening of blood spot 17OH-progesterone concentrations.

Clinical features

CAH is subdivided into classical forms (virilization presenting early, with or without salt loss) and non-classical forms (late-onset forms presenting in late childhood or adolescence). Table 1 summarizes the different modes of presentation according to age, key modes being:

- ambiguous genitalia in an affected female newborn
- a salt-losing crisis in a male newborn
- a syndrome of hirsutism, acne and irregular periods in an adolescent/adult female patient.

The diagnosis is confirmed by elevated concentrations of serum 17OH-progesterone (often ≥300 nmol/litre (normal <10 nmol/litre)) and testosterone, which can be in the adult male range (10–30 nmol/litre). Hyponatraemia and hyperkalaemia indicate a salt-losing crisis, and there can also be hypoglycaemia. In the late-onset form of CAH, the diagnosis is confirmed by demonstrating an exaggerated 17OH-progesterone response to short-acting ACTH stimulation. Genetic analysis is performed to identify the specific *CYP21A2* mutations, to confirm the diagnosis. There is a reasonable concordance between genotype and phenotype during infancy and childhood, but less so in adulthood, mainly as a result of an acquired impairment in health status. Once a genetic diagnosis is known, cascade screening can be performed in the family and in partners to determine the risk for future children.

Management

Infancy

When the external genitalia are ambiguous in appearance, the underlying cause must be ascertained as soon as practicable to reach a decision with the family about sex assignment. Demonstrating that the sex chromosomes are XX by fluorescence *in situ* hybridization and karyotype analysis, together with an elevated

Clinical presentation of CAH

Age	Sex	Presentation
Infancy	F	Ambiguous genitalia
	M/F	Salt loss
Early childhood	M	Virilization, rapid growth
Late childhood	F	Early pubic hair, rapid growth
Adolescence/young adult	F	Delayed menarche, irregular menses, acne, hirsutism, infertility
	M	Testicular masses, infertility

F, female; M, male.

Table 1

© 2017 Published by Elsevier Ltd.

Please cite this article in press as: Simpson H, Hughes I, Congenital adrenal hyperplasia, Medicine (2017), http://dx.doi.org/10.1016/j.mpmed.2017.05.012

Download English Version:

https://daneshyari.com/en/article/5681130

Download Persian Version:

https://daneshyari.com/article/5681130

Daneshyari.com