Congenital adrenal hyperplasia

Management strategies in children and adults

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Congenital adrenal hyperplasia is a complex and varied condition requiring specialist input and long-term review. However, the GP has a major role in suspecting an adrenal cause for presentations such as early pubarche or virilisation, unusually rapid growth in a child, early and severe polycystic ovary syndrome, fertility issues and testicular masses in men. The necessary investigations and specialist referrals can then be carried out, and the correct management strategies shared between the GP and specialist can be put in place.

Key points

- **Congenital adrenal hyperplasia (CAH) can present as an endocrine emergency in an infant with vomiting and/or ambiguous genitalia.**
- **CAH should be considered in a tall, rapidly growing boy or girl with premature pubic hair.**
- **Nonclassical CAH (NCCAH) may present for the first time as apparent polycystic ovary syndrome (PCOS).**
- **Treatment requirements for CAH vary at different times of life and with different types of CAH.**
- **Treatment of CAH is different from standard treatment of adrenal insufficiency and requires specialist consultation.**
- **Most adults with CAH are potentially fertile, but fertility may be complicated by PCOS or adrenal rest tissue.**

Congenital adrenal hyperplasia (CAH) is the most common adrenal disorder of childhood. In Australia, the carrier state is one in 50, with one in 14,500 infants affected, although gene frequency varies between ethnic groups.

CAH is caused by an abnormal mutated gene, with autosomal recessive inheritance, on chromosome 6, adjacent to the gene for the HLA complex. This results in variable deficiency of an enzyme, most commonly 21-hydroxylase, due to a mutation in the *CYP21A2* gene, in the cascade of adrenal steroid biosynthesis. Many different mutations are recognised. Deficiency of 21-hydroxylase accounts for nearly 95% of all cases of CAH, with other rare enzyme defects comprising the remaining 5% (Box 1).

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CAH due to 21-hydroxylase is categorised into two major types, classical and nonclassical, depending on the symptoms. Classical CAH is further classified into salt-wasting and simple virilising forms although they are really just more or less severe manifestations of the enzyme deficiency.

Adrenal steroid biosynthesis and CAH

The complex cascade of steroid production is shown in Figure 1, demonstrating the enzymes that control each step in the pathway. Whenever an enzyme is absent or reduced in activity, the product prior to the block in steroid production rises.

Cholesterol is converted into steroid hormones by a number of enzymes in this biosynthetic pathway in the adrenal glands, gonads and placenta. In the adrenal glands, aldosterone is produced from the outermost layer, the zona glomerulosa, cortisol is produced from

the zona fasciculata, and androgens from the innermost layer, the zona reticularis. The inner zones that produce cortisol and androgens are controlled by adrenocorticotrophic hormone (ACTH), whereas the outer zona glomerulosa is controlled by the renin–angiotensin system. Elaboration of cholesterol to pregnenolone is controlled by ACTH and is the rate-limiting step in mitochondria, with later products of androgens produced outside the mitochondria.

Clinical features of CAH vary with the degree of enzyme deficiency and with the sex of the patient. Impaired biosynthesis of cortisol and aldosterone occur as a consequence of impaired or absent enzyme activity, but androgen secretion is not disturbed. ACTH levels rise in response to a lack of cortisol production, the fetal adrenal glands become hyperplastic and androgen secretion is stimulated, resulting in masculinisation of female genitalia before birth.

About Quincy (the girl in the cover image)

Quincy (nickname: The Flying Squirrel) is 6 years old and was diagnosed with classical salt-wasting congenital adrenal hyperplasia (CAH) at birth, after being transferred from a country hospital to Melbourne Royal Children's Hospital. She has deficiency of the 21-hydroxylase enzyme, which accounts for nearly 95% of all cases of CAH.

Quincy and her family have a great team of doctors, including her local GP, paediatrician and endocrinologist, to help with ongoing treatment and monitoring of her condition.

Quincy loves being outdoors and leads a very active and full life. She has a love for music and is a massive football fan. Her favourite hobbies are surfing, skate boarding and golf, and her goal in life is to become a professional surfer.

Note: Quincy is not a patient of Dr Zacharin.

1. Rare enzyme causes of CAH

11β-Hydroxylase deficiency
This is the most frequently seen of the rare disorders, with a defective enzyme at the last step of cortisol biosynthesis. Cortisol and aldosterone levels are reduced but deoxycorticosterone (DOC) is present. Virilisation occurs but salt loss is counteracted by the presence of DOC. Although infants may experience an adrenal crisis in later months and in future years, DOC predominates and arterial hypertension becomes a serious problem. By contrast, early enzyme defects in the steroid synthetic cascade reduce secretion of some or all adrenal steroids and usually result in the clinical appearance of an undervirilised male.

17α-Hydroxylase deficiency
This deficiency results in a lack of all sex steroids in the testes or ovaries, causing a female phenotype. Cortisol levels are low but corticosterone and DOC levels are high, causing hypertension.

Lipoid adrenal hyperplasia
This condition is due to a lack of the steroidogenic acute regulatory protein (StAR) in the mitochondria, blocking entry of cholesterol into the mitochondria. As a result all adrenal and gonadal steroid biosynthesis is blocked and a female phenotype with salt wasting occurs.

3β-Hydroxysteroid dehydrogenase deficiency
This results in virilisation of females with excess adrenal androgens but impaired virilisation of males because adrenal androgens are less potent than testosterone. Severe salt wasting at birth may occur.

18-Hydroxylase deficiency
This is a very rare cause of CAH with salt wasting due to a block in aldosterone biosynthesis but with preservation of cortisol and androgen biosynthesis.

17β-Hydroxysteroid dehydrogenase deficiency
This condition is not strictly a congenital adrenal hyperplasia but results in undervirilisation of males. It is not associated with glucocorticoid or mineralocorticoid loss so often presents later in life.

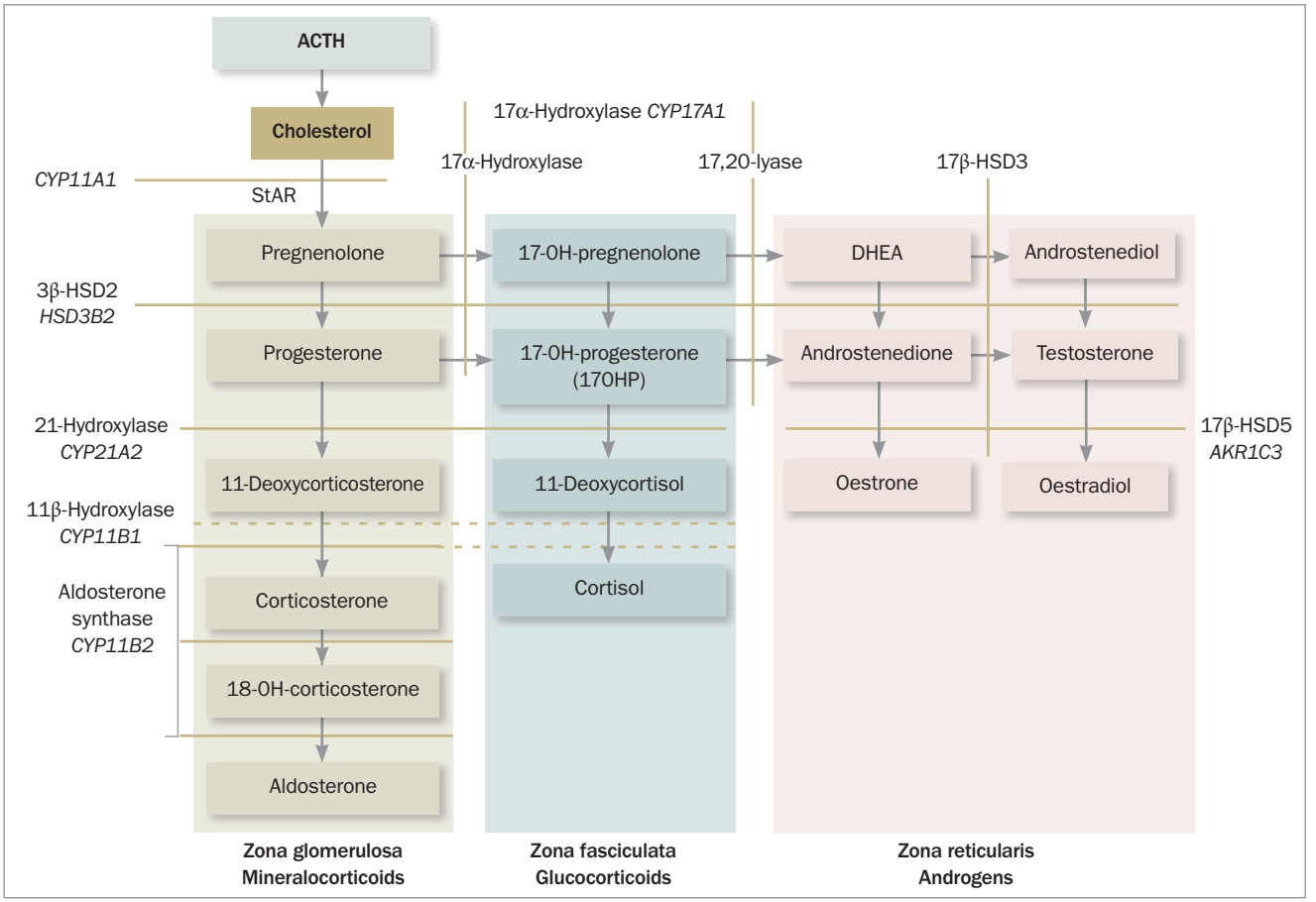

Figure 1. Adrenal steroidogenesis pathway.

Abbreviations: ACTH = adrenocorticotrophic hormone; DHEA = dehydroepiandrosterone; HSD = hydroxysteroid dehydrogenase; StAR = steroidogenic acute regulatory protein.

CAH at birth

Salt-wasting CAH

Clinical features of classical CAH at birth include genital ambiguity with impalpable gonads in female infants. Hyperpigmentation due to excess ACTH may be seen at birth but may take days or even weeks to develop. Even with severe salt-wasting CAH, the baby is usually quite healthy and only develops the effects of cortisol and aldosterone deficiency seven to 10 days after birth in most cases, presenting with poor feeding, vomiting, dehydration and shock if the cause is not recognised. These events are accompanied by biochemical features of glucocorticoid and mineralocorticoid insufficiency, with hypoglycaemia, hyponatraemia, hyperkalaemia and mild haemoconcentration. The presentation of CAH at birth and the investigations required are shown in Box 2.

Treatment of an infant with CAH

Acute rehydration with sodium chloride and glucose is required for infants with salt-wasting CAH, together with intravenous hydrocortisone. Once stabilised, maintenance management is with hydrocortisone 10 to 14 mg/m^2/day in three doses, plus fludrocortisone 0.1 to 0.2 mg/day. Most infants require additional salt supplementation for three to six months until the renin–angiotensin system is established. Education of parents and/or guardians is essential (Box 3). Monitoring of the long-term management of CAH in childhood is outlined in Box 4.

Surgery for affected girls

Surgery may be needed for girls with virilisation. In recent years there has been great discussion as to the best timing and type of procedure to be performed. Current guidelines for surgery are detailed in the Table.[1-3]

Surgery involves clitoral reduction, aiming to preserve nerve and blood supply to the glans, but removing tissue with engorgement capacity, together with recessing and placing the glans at the 'normal' anatomical site. A single stage procedure including introital surgery, where there is labial fusion, is performed in some centres but this procedure may be delayed until later childhood or early adolescence, prior to menarche. Although excellent outcomes are reported in specialised centres treating these infants, a number of reports indicate the need for repeated surgery and unsatisfactory results, with the vaginal introitus reported as inadequate in 35 to 90% of cases.[4]

Concerns have resulted in investigations by the Australian Human

2. Presentation and investigations of CAH at birth

Presentation

Infant with ambiguous genitalia, with or without pigmented genitalia and nipples, starts to vomit after 1 week of age.

Infant boy presents with vomiting and adrenal crisis at 2 to 3 weeks of age, occasionally even later at 2 to 3 months.

Investigations

Immediate investigations include measurement of blood glucose levels, serum electrolytes and urea (looking for low sodium, high potassium and high urea levels) and fluorescent in situ hybridisation (FISH) test for Y chromosomal material.

Karyotyping will help define a 46XX female with virilisation rather than 46XY undervirilised male or other rare problems unrelated to adrenal insufficiency. This is only needed if testes are not palpable.

Definitive tests: measurement of 17-hydroxyprogesterone and urine steroid profile (gas liquid chromatography or mass spectrometry) where available. These should be performed at or after day three of life to reduce interference from maternal steroids.

Pelvic ultrasound, for female internal genitalia (uterus/ovaries). Genitoscopy, for internal genitalia structures and presence of vagina. In some centres, MRI is used.

3. Education of parents and/or guardians

- Patients should not stop taking steroids without expert medical advice.
- The hydrocortisone dose should be tripled for two to four days during fever or other acute illness, followed by double the dose for three days.
- Hydrocortisone should be given by injection if the patient is unable to tolerate by mouth (due to vomiting, diarrhoea).
- Injection of hydrocortisone (25 to 100 mg depending on age) should be given before any surgery under general anaesthetic.
- It is recommended that patients wear an ID bracelet or pendant stating the disorder and how to treat it or where to find information.
- Re-education of parents is needed after any adrenal crisis.
- For information on CAH for families, see: *Hormones and me: congenital adrenal hyperplasia*, available through the Australasian Paediatric Endocrine Group website (www.apeg.org.au/Portals/0/resources/Hormones_and_Me_8_CAH.pdf).

4. Monitoring of long-term management of CAH in childhood

- Linear growth velocity, ideally every three to four months
- Assessment for excessive weight gain
- Blood pressure
- Sexual development
- 0900 h 17-hydroxyprogesterone, plasma renin activity (PRA), performed before morning medication, for consistent interpretation
- Bone age

Rights Commission, the Victorian health department and an Australian Senate Inquiry, among others. A consensus statement on the management of CAH was published some years ago, but management planning continues to be challenging.[5]

Long-term female outcomes of CAH

Although most children with CAH in Australia grow up to be healthy, well-adjusted adults, reports exist where gender role behaviour (tomboys) may be affected. Sexual orientation may also be affected. Sexual identity is rarely altered but may be if the girl has been under-treated during childhood over a long time. Women with CAH have been reported as less sexually active than other women.

In the past, fertility was reduced in women with salt-wasting CAH. However, with better long-term treatment and improved understanding and treatment strategies for secondary polycystic ovary syndrome (PCOS), most women with CAH can now expect to be fertile.

Prenatal genetic testing and treatment

Once a proband is identified with CAH, a recurrence risk for an autosomal recessive condition is 1:4, with an affected female risk of 1:8. Prenatal genetic diagnosis is available through amniocentesis. Thus, the question arises of whether a pregnant woman should be offered treatment to prevent virilisation of an infant.

Prenatal dexamethasone has been used from confirmation of pregnancy until a firm diagnosis of CAH has been reached and continued to term for an affected female fetus. Such treatment can prevent the need for surgery in 80% of affected females. However, first-trimester use of dexamethasone in animals has been reported to result in reduced birth weight and adverse effects on renal, pancreatic beta cells and brain development, and to predispose to adult hypertension and hyperglycaemia. In humans it has been associated with orofacial clefts, low birth weight, and poorer verbal working memory, self-perception and scholastic and social competence.[6]

Current recommendations for prenatal treatment of CAH with dexamethasone are as follows:

- it should only be carried out in prospective clinical research settings
- it should only be carried out with institutional review board approval
- it is not appropriate for routine community practice.

Simple virilising (nonsalt-wasting) CAH

Late presentation of less severe enzymatic defects known as simple virilising CAH (also called nonsalt-wasting CAH) is part of a spectrum of enzymatic deficit, with either mild mutations on both alleles of the 21-hydroxylase locus or one mild plus one severe mutation (compound heterozygote). With this form of CAH, levels of cortisol are reduced, but the degree of aldosterone deficiency is not as extreme and there is no salt wasting. This form of CAH also causes ambiguous genitalia in girls and virilisation in both sexes before puberty.

Table. Current recommendations for surgery in girls with CAH

	Chicago consensus[1]	Endocrine society[2]	Lee et al, 2012[3]
Severity	Prader scale 3+		
Timing	Early, but late option (e.g. delayed vaginoplasty)	Debatable early or late, clitoroplasty may be separated from vaginoplasty	Delayed clitoroplasty for at least Prader 3
Timing of consent	Consequences throughout life	May have poor long-term prognosis for sexual and reproductive function, offer deferring of surgery	May have poor long-term prognosis for sexual and reproductive function, offer deferring of surgery
Experience	Surgeon specialising in disorders of sex development in a high-volume centre		
Follow up	Long-term follow up of surgery required		

The author wishes to acknowledge Dr Jacqueline Hewitt, Paediatric Endocrinologist in Melbourne, for the summary in this Table.

5. Investigations for nonclassical CAH

These are usually performed in consultation with an endocrinologist.

- Androgen screen
- Measurement of 17-hydroxyprogesterone, testosterone and androstenedione levels
- Short Synacthen test, measuring 17-hydroxyprogesterone levels at 0 and 60 minutes
- Karyotyping indicated if no uterus is seen on ultrasound
- Increased luteinising hormone to follicle-stimulating hormone ratio >2:1 (as a guideline for polycystic ovary syndrome)
- Pelvic and abdominal ultrasound to exclude adrenal or ovarian tumours

Presentation may be in late infancy or early childhood, with clitoral enlargement in a girl who may be tall, muscular, hyperactive and aggressive, or a boy who presents with sexual precocity but no testicular enlargement because of excess androgens from the adrenal gland (not the testes).

Nonclassical CAH (or late-onset CAH)

Nonclassical CAH (NCCAH) has been recognised since 1979. Presentation of both males and females with NCCAH varies, from unusually tall stature in a family, premature pubic hair (pubarche) and advanced bone age to less obvious features suggesting androgen excess such as premenarchal acne. There is no genital ambiguity, no salt wasting and normal aldosterone levels. Investigations for NCCAH are outlined in Box 5.

Clinical features of NCCAH in females

Presentation of NCCAH in females can be delayed until after puberty and has a similar picture to PCOS, with hirsutism, acne, menstrual irregularity and/or male pattern baldness. A high index of suspicion for NCCAH should exist in the following situations:

- premenarchal or early postmenarchal acne with poor response to standard antibiotic treatment
- history of isotretinoin treatment with relapse
- hidradenitis suppurativa
- poor breast growth, delayed menarche or severe oligomenorrhoea.

Very late presentation may occur if a girl has been treated from early teenage years for these complaints with the oral contraceptive pill. Thus symptoms and signs only become obvious when the pill is ceased.

Clinical features of NCCAH in males

Most men with NCCAH are asymptomatic but are likely to be relatively tall during childhood although they have a reduced adult height. Premature adrenarche and pubic hair without testicular enlargement should alert the examiner to androgen excess from a nontesticular site. For a boy with this presentation, an androgen-secreting tumour must be excluded. In adulthood, mild oligospermia and adult infertility may be due to NCCAH.

Rare presentations of NCCAH

People with 11β-hydroxylase deficiency may present late with progressive virilisation and hypertension. Those with other rare disorders of adrenal enzyme production can also present late with either progressive virilisation of a phenotypic female or undervirilisation of a male.

Presenting features of 17β-hydroxysteroid dehydrogenase deficiency include tall stature, progressive virilisation of a phenotypic female and likely gender identity change if not identified prior to puberty. However, cortisol production is not affected. It can be confused with 11β-hydroxylase deficiency (Box 1).

Is a diagnosis of NCCAH necessary?

A correct diagnosis of NCCAH improves family understanding, provides a rational path for management, reduces massive costs of commercial acne treatment and hair removal methods, improves outcomes, and reduces emotional and financial cost to families and patients.

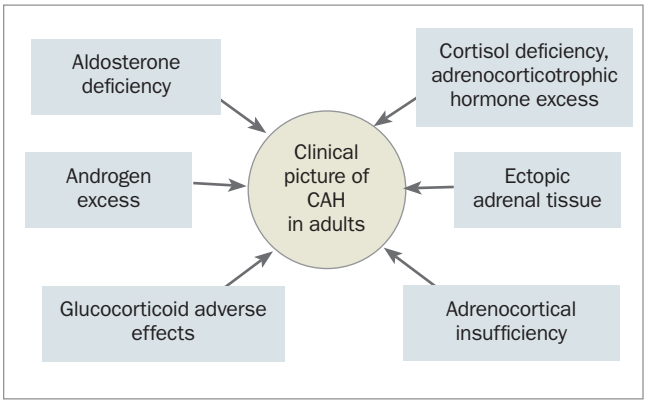

Figure 2. Clinical picture of congenital adrenal hyperplasia (CAH) in adults.

6. Clinical features of poorly controlled CAH in adult men

- Tiredness
- High salt intake
- Skin pigmentation (palmar crease, scars, nipples)
- Relative short stature in family
- Slow, progressive weight loss
- Acute presentation with collapse at time of intercurrent surgery, fracture or serious illness, with or without abdominal pain
- Hypotension, decreased sodium level, increased potassium level

Treatment of NCCAH

Glucocorticoid replacement is the obvious rational answer for the treatment of NCCAH but it is usually not required unless bone age advance is very severe and truncation of final height is a concern. As the enzyme deficiency is relatively mild, concerns arise that corticosteroids will suppress residual normal cortisol production, leading to risk of an adrenal crisis in a child who was previously independent of need for care.

No treatment may be needed in childhood but symptomatic treatment is usually recommended in adolescent girls, using androgen blockade and ovarian suppression, with spironolactone 1 to 200 mg/day and a non-norgestrel containing contraceptive pill. Treatment during pregnancy is unnecessary. Institution of corticosteroids in children with NCCAH is biochemically effective but usually results in weight gain and an unhappy patient (and parents).

Consideration for treatment of boys with NCCAH may be needed as male oligospermia and male infertility have been reported. Use of growth hormone plus luteinising hormone-releasing hormone agonists to improve final height in affected children has been advocated but is experimental, with no convincing evidence for efficacy.

CAH in adulthood

Adequate treatment of adults with CAH differs from treatment of other causes of adrenal insufficiency. In addition to glucocorticoid and mineralocorticoid replacement, the additional problem of control of androgen excess is required (Figure 2). There is little correlation between genotype, phenotype and corticosteroid needs,[7] and impaired health of adults with CAH is acquired rather than genetically determined.

As with all patients requiring long-term corticosteroid replacement, precise titration of dose may be relatively inaccurate and relative steroid excess over many years can result in reduced bone density. Excess weight has adverse consequences for cardiovascular risk and obesity. A recent report of a large cohort of adults with CAH suggested that at least one-third to one-half of people with this condition experience these complaints.[8] In addition, women with CAH may have issues related to fertility, pregnancy, sexual function and psychological concerns. Men may have testicular abnormalities and infertility.

Adult men with CAH

Male infant virilisation is of less concern for families. Surgery is never required and uneventful childhood progress is likely if suitable steroid replacement is administered. In both sexes there is a tendency for less salt loss with time, so boys become able to tolerate reduced or intermittent steroids. Compliance is a major issue, medication omission is common and may be ignored by families. However, consequences of long-term underdosing are severe, with premature epiphyseal fusion and relative short stature. Permanent infertility may result. Clinical features of poorly controlled CAH in adult men are listed in Box 6.

Fertility and testicular problems in adult males with CAH

Testes grow normally during puberty in boys with CAH. Excess adrenal androgens lead to abnormal feedback, reduced secretion of central luteinising hormone and follicle-stimulating hormone and consequent hypogonadotrophic hypogonadism, with resulting infertility but with normal adult male testes size.

In adult men with CAH, adrenal rest tissue is frequently found in the testes, which grow larger than normal (40 to 50 mL) because of chronic ACTH over stimulation. Lesions can be large and palpable with disseminated calcific deposits and progressive loss of testis function. Presentation for care is late, with time between documentation of clinically abnormal testes and infertility between 0 and 10 years. Testicular adrenal rest tumours (TARTs) have a typical ultrasound appearance (Figure 3). They are usually bilateral with hypo- and hyperechoic lesions located near the mediastinum testis without distortion of testicular contours. They may develop independently of long-term disease control[9] but are usually seen with chronic poor control of CAH. It is of utmost importance to differentiate TARTs from Leydig cell tumours. Testicular enlargement from TARTs is often misdiagnosed as malignancy because these tumours give the testis a rock hard texture. Surgical removal of testis has been reported in cases in which TARTs have erroneously been considered to represent cancer.

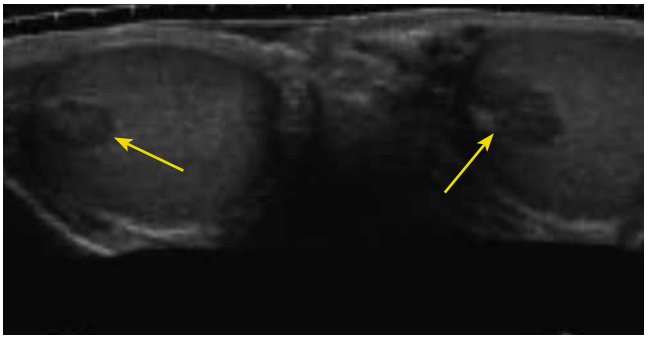

Figure 3. Testicular adrenal rest tissue (arrows).

Possible treatment of TARTs

Postpubertal ultrasonography every three to five years is helpful for all adolescent boys and men with CAH to monitor future fertility and assist with decisions regarding their management.

Testis sparing surgery may improve outcomes of infertility. Dexamethasone suppression of adrenal androgen excess can increase spermatogenesis and reduce adrenal rest tissue but only reverses infertility in some cases. Successful pregnancy outcome has been reported with different treatment modalities, including change of treatment to dexamethasone for better ACTH suppression, excision of rest tumours and intracytoplasmic sperm salvage. However, normal testicular volume, gonadotrophin levels, adrenal biochemistry and testicular ultrasound do not predict normal spermatogenesis or semen quality. Semen analysis is necessary.

Treatment of adults with CAH

Treatment goals for adults with CAH should aim to mimic physiological steroid secretion. Many different regimens are used, including prednisolone, hydrocortisone and occasionally dexamethasone (see Box 7). If adrenal androgen suppression is needed, hydrocortisone dosing must be three times daily, due to its short duration of action. Prednisolone is often more convenient for adults with CAH due to its longer-acting profile but should not usually be used if growth potential remains because it suppresses linear growth, as does dexamethasone. Most women cannot tolerate dexamethasone because it usually causes severe weight gain, but men may find the single daily dosing schedule easier, with better compliance.

Bilateral adrenalectomy has been considered as an alternative stratagem with a rationale to eliminate excess adrenal steroid precursors and need to suppress ACTH, allowing reduced glucocorticoid levels. It is considered experimental and precludes possible options of new medical approaches.

A recent publication from a large cohort of adults with CAH in the UK reported no consensus on the management of CAH beyond childhood, with only 10% of adult patients with CAH under the care of endocrine centres.[10] Varied corticosteroid and mineralocorticoid regimens were prescribed but less than one-third of patients reported good control, with obesity, osteoporosis, and impaired fertility and sexuality in many patients.[7] As a result of inconsistent and difficult care, many patients stopped treatment altogether out of frustration. This article defined some very important points, many of which may apply to adults with CAH in Australia. Not only are physiological requirements different from patients with Addison's disease and adult needs are obviously distinctly different from those of children, but training of medical staff and even adult endocrine trainees is inadequate to address management and monitoring strategies that are "unorthodox and foreign to most practitioners".

7. Common regimens for treating CAH in adults

- Prednisolone 5 to 10 mg/day in two divided doses
- Dexamethasone 0.25 to 0.5 mg/day
- Hydrocortisone 15 to 45 mg/day in three divided doses
- Fludrocortisone 0.05 to 0.1 mg/day if salt loss persists

Role of the GP

The GP plays a central role in the management of these complex patients by suspecting an adrenal cause for problems such as early pubarche or virilisation, unusually rapid growth in a child, early and severe PCOS, fertility issues in men and women, and testicular masses in men. Knowledge about CAH therefore allows appropriate basic diagnostic tests to be carried out and patients to be referred to specialists early. Subsequent care can then be shared between the specialist and the GP, with safe management of acute ill health, appropriate use of steroid cover for stress where needed and supportive management through sensitive times of adolescence and early adulthood where medication compliance and the transfer of education and information from parent to patient is so crucial.

Conclusion

CAH is a complex and varied condition with presentations ranging from perinatal emergencies, infant and childhood virilising disorders in girls or more rarely undervirilisation in boys, through to apparent PCOS, testicular masses and fertility impairment. Knowledge of the pathways of steroid biosynthesis and consequent defects in this developmental cascade can alert the practitioner to undertake a more diligent search for an underlying cause when an infant, child or adult presents for assessment of these problems. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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