Personal practice

Management of congenital adrenal hyperplasia

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Congenital adrenal hyperplasia is the commonest adrenal disorder in infancy and childhood and results from a deficiency in the activity of one of the five enzymes required for cortisol biosynthesis.[1] More than 90% of cases are due to a deficiency of 21-hydroxylase enzymes required for the conversion of 170H-progesterone to 11-deoxycortisol and of progesterone to 11-deoxycorticosterone. The inheritance is autosomal recessive and the monogenic trait is closely linked to the HLA locus on chromosome 6.[2] A further 5% of cases are associated with a deficiency of the 11β-hydroxylase enzyme involved in the terminal steps of cortisol and aldosterone biosynthesis. The clinical hallmark of both enzyme defects is virilisation consequent upon increased adrenocorticotrophic hormone secretion causing excess adrenal androgen production. The remaining enzyme defects causing congenital adrenal hyperplasia are very rare and their management is not discussed.

Clinical presentation

Fetal adrenal steroidogenesis is established in early gestation so that a female fetus with congenital adrenal hyperplasia invariably has virilised external genitalia at birth. The degree of virilisation can range from mild isolated clitoromegaly or partial labial fusion to complete fusion of the labioscrotal folds ('scrotalised' labia) and pronounced clitoromegaly with a phallic urethra. The latter variant may masquerade as a cryptorchid 'male' with or without hypospadias. The consequences of inappropriate gender assignment can be tragic when the true sex is realised in later life.[3] The clitoris and labia minora may be sufficiently prominent in an otherwise normal preterm female infant to raise a suspicion of partial virilisation of the genitalia. Sometimes an affected girl does not show signs of virilisation at birth. This late onset variant of congenital adrenal hyperplasia usually presents with the onset of early pubic or labial hair growth and accelerated linear growth. A boy with congenital adrenal hyperplasia

rarely has signs of virilisation at birth despite plasma testosterone concentrations which are often within the normal adult male range. Increased pigmentation of the scrotal skin may sometimes be a clue to the diagnosis. Typically the affected boy is recognised as the result of a salt losing crisis, which presents during the second or third week of life. A mistaken diagnosis of pyloric stenosis has been made occasionally but the electrolyte pattern should distinguish the two disorders. Many families with patients who have congenital adrenal hyperplasia report a history of previous unexplained male infant deaths.[4] It is my impression that with the increased awareness of the disorder by paediatricians, and the availability of rapid diagnostic tests, cases of salt losing congenital adrenal hyperplasia are now rarely missed in this country.

About one third of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency are non-salt losers. Males with this form of congenital adrenal hyperplasia are not clinically detected at birth and show signs of virilisation in late infancy and childhood. The signs include growth of the penis and pubic hair, increased muscle bulk, and rapid linear growth. The testes remain prepubertal in size. This is an important clinical sign to indicate that the increased androgen production arises from a peripheral (adrenal) source which is independent of central gonadotrophin stimulation. It is now recognised that there is a wide range of clinical manifestations of 21-hydroxylase deficiency. The examples are summarised in table 1. A simple classification into classical and non-classical forms of congenital adrenal hyperplasia has been proposed based on phenotype (symptomatic or asymptomatic).[5] In classical congenital adrenal hyperplasia, there is prenatal virilisation, which may also be accompanied by early postnatal salt wasting. Non-classical congenital adrenal hyperplasia includes patients with postnatal or late onset virilisation or those who are asymptomatic but show abnormalities on biochemical testing. These are referred to as cryptic cases in table 1 and are usually identified when relatives of an index case

Table 1 *Clinical manifestations of 21-hydroxylase deficiency*

Newborn	Later life
Ambiguous genitalia:	Pseudoprecocious puberty
Complete	Isolated pubarche
Isolated clitoromegaly	Isolated clitoromegaly
Isolated labial fusion	Rapid growth
	Hirsutism
Cryptorchid, hypospadic 'male'	Menstrual disorders
	Infertility
Salt wasting	Cryptic cases

with classical congenital adrenal hyperplasia are investigated.

Girls with congenital adrenal hyperplasia due to 11β-hydroxylase deficiency are also virilised at birth and the degree may be more severe than in the 21-hydroxylase defect. Salt wasting is not a feature of untreated 11β-hydroxylase deficiency and affected boys are only recognised in later infancy and childhood because of early signs of pseudoprecocious puberty. Prepubertal gynaecomastia is another feature peculiar to this enzyme defect. The clinical hallmark of 11β-hydroxylase deficiency is hypertension secondary to increased mineralocorticoid production. Hypertensive encephalopathy and cerebrovascular accidents are known complications but the severity of hypertension is unrelated to the degree of virilisation.[6] Hypertension is not a constant feature of 11β-hydroxylase deficiency, however, and is rarely present at birth.

Diagnosis

The newborn infant with ambiguous genitalia is a medical emergency and appropriate investigations must be started quickly. The problem is a distressing one for the parents and they must be given a careful explanation of what will be done to determine the sex of the infant and how long this will take. There must be no guessing at the sex. It is important to note that the commonest cause of ambiguous genitalia of the newborn is congenital adrenal hyperplasia and the commonest cause of congenital adrenal hyperplasia is 21-hydroxylase deficiency. To confirm this diagnosis two investigations are essential: measurement of plasma 170H-progesterone concentration and determination of a peripheral karyotype. A complete list of relevant investigations is shown in table 2.

The enzyme 21-hydroxylase is required for the conversion of 170H-progesterone to 11-deoxycortisol in the pathway of cortisol biosynthesis. In its absence there is accumulation of 170H-progesterone,

which is readily measured in plasma. The test is rapid and reliable for the diagnosis of 21-hydroxylase deficiency.[7 8] The assay is available routinely through the supraregional steroid assay service and can be performed on filter paper blood spots as well as in plasma, saliva, and amniotic fluid. It is advisable to delay sample collection for 24 hours after birth to allow for the disappearance in 170H-progesterone produced by the placenta. The steroid is a stress related hormone and concentrations can be very high in ill infants (particularly if preterm) without adrenal disease.[9] A repeat measurement of 170H-progesterone when the infant is better or an assessment of the 170H-progesterone response to adrenocorticotrophic hormone stimulation may be necessary to resolve the question of possible 21-hydroxylase deficiency in a male preterm infant with low plasma sodium concentrations.

The peripheral karyotype must always be determined in an infant with ambiguous genitalia or in a 'male' with bilateral cryptorchidism and hypospadias. A provisional result can be provided by most cytogenetic laboratories within 48 hours of lymphocyte culture. A definitive diagnosis of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in a newborn infant with ambiguous genitalia can be made two to three days after birth based on a 46 XX karyotype and an increased plasma concentration of 170H-progesterone (usually >200 nmol/l; normal <10 nmol/l in a full term infant). Other steroid concentrations known to be raised in 21-hydroxylase deficiency include 21-deoxycortisol, androstenedione, and testosterone. When the plasma 170H-progesterone concentration is normal or only slightly increased, the concentration of plasma 11-deoxycortisol as an index of 11β-hydroxylase deficiency should be determined. Additional confirmatory evidence of this rarer enzyme defect can be obtained by measurement of specific steroid metabolites in urine using detailed gas chromatographic analysis.

Table 2 *Diagnostic tests for congenital adrenal hyperplasia*

Blood:	170H-progesterone
	Testosterone
	Androstenedione
	Adrenocorticotrophic hormone
	Plasma renin
	11-Deoxycortisol (11β-hydroxylase defect)
	Karyotype
Urine:	17-Oxosteroids
	Pregnanetriol
	Gas chromatographic steroid profile
Radiology:	Pelvic ultrasound examination
	Vaginography
	Intravenous urography

Plasma concentrations of adrenocorticotrophic hormone are raised with both enzyme defects but the assay is available only in a few specialised centres. Ambiguous genitalia in an infant with a 46 XY karyotype is a complex problem requiring investigation by a paediatric endocrinologist.

At least two thirds of patients with 21-hydroxylase deficiency are salt losers. Typically they develop hyponatraemia, hyperkalaemia, azotaemia, early metabolic acidosis, increased urinary sodium excretion, and occasionally hypoglycaemia. Plasma renin activity is a more sensitive index of mineralocorticoid insufficiency and is increased soon after birth.[10] However, the results are seldom available immediately.

Early management

MEDICAL

The salt losing crisis in an infant with congenital adrenal hyperplasia requires treatment with intravenous normal saline, the amount being calculated based on the sodium deficit and the degree of dehydration. Glucose should also be infused because of the risk of hypoglycaemia. Hyperkalaemia may rarely be severe enough to require more immediate treatment with insulin. Unless there is peripheral circulatory collapse, glucocorticoids should be withheld until blood samples for steroid analyses have been collected. Glucocorticoid treatment can be started using a replacement dose from the onset; this will adequately suppress raised 17OH-progesterone concentrations within weeks. The alternative regimen of using a high initial dose of glucocorticoid is unnecessary and almost certainly adversely affects the normal rapid growth rate characteristic of early infancy. I favour the use of hydrocortisone (cortisol) as the preferred choice of glucocorticoid. It is the physiological hormone active in man, the cortisol secretion rate is standardised for surface area (about 12 mg/m²/day),[11] and there is 50% consistent absorption of an oral dose. A dose of 20 mg/m²/day is about 5 mg per day for an infant; this can be divided into dosages of 2·5, 1·25, and 1·25 mg given at intervals of eight hours. The pharmacist will need to prepare hydrocortisone in solution to prescribe such small amounts. An oral preparation of cortisol (Corlan, Glaxo) in the form of 2·5 mg hydrocortisone pellets designed for treating mouth ulcers can be prescribed after the first year.

Salt replenishment during the early salt losing crisis is usually adequately provided by intravenous saline. It is seldom necessary to use a parenteral mineralocorticoid preparation. Oral 9α-fludrocortisone (Florinef) is a potent mineralocorticoid which can be started in a dose of 0·1–0·2 mg daily once the infant is rehydrated and taking oral feeds. Occasionally higher doses are required but the blood pressure must be monitored regularly. Supplementing the oral feeds with 2–3 g of salt daily in divided doses until semisolid feeding is established is occasionally required.

Deoxycortisone pivalate is a long acting mineralocorticoid which, in a dose of 12·5–25 mg monthly by intramuscular injection, is useful for the rare patient in whom there is a problem with treatment compliance.

SURGICAL

The variable degree of virilisation of the external genitalia in girls with congenital adrenal hyperplasia has already been emphasised. It is essential for the infant to be seen early by a surgeon experienced in the techniques required for reconstruction of the genitalia. There are basically two structural abnormalities which require surgical treatment: reduction in the size of the enlarged clitoris and division of the fused labial folds to exteriorise the vaginal opening. The various surgical techniques used to perform the clitoroplasty and vaginioplasty are beyond the scope of this review. Some or all of the radiological investigations listed in table 2 should be performed before surgery. Only clitoroplasty is normally performed in infancy; unless there is evidence that the labial fusion and urogenital sinus is contributing to infection, it is preferable to delay vaginoplasty until the time of puberty. The parents should understand that the female internal genitalia are normally developed. Pictures from a pelvic ultrasound examination or vaginography to show the uterus and ovaries can be most reassuring. The sex of rearing for a girl with congenital adrenal hyperplasia should always be female, whatever the degree of virilisation.

Later management

Treatment in congenital adrenal hyperplasia should aim to ensure normal growth in infancy and childhood, the development of puberty at the appropriate age and later, the acquisition of adult reproductive potential. This goal needs to be achieved using the minimum amount of glucocorticoid required to suppress excess androgen production. There is a delicate balance to strike between the prevention of androgen induced rapid growth with advanced skeletal maturation on the one hand and the inhibition of normal growth from excessive glucocorticoid replacement on the other.

Several glucocorticoid preparations have been tried as regular replacement treatment in congenital adrenal hyperplasia. Their relative potencies in

Table 3 *Potency of steroid preparations used in congenital adrenal hyperplasia*

Steroid	Potency
Cortisol	1·0
Cortisone	0·8
Prednisolone	5·0
Prednisone	4·0
Dexamethasone	80·0
9α-Fludrocortisone	10·0

Cortisol is arbitrarily assigned a value of 1 for glucocorticoid potency.

relation to cortisol (hydrocortisone) are shown in table 3. I favour the continued use of hydrocortisone throughout childhood and puberty until statural growth is almost complete. A dose as low as 12–15 mg/m^2/day is often sufficient but the treatment for each individual needs to be tailored according to age appropriate growth rates and various steroid indices of control (see later). The daily amount of hydrocortisone needs to be given in two or three divided dosages; it is customary to administer 50% of the daily dose at bedtime but there is no evidence that this achieves any better control. Cortisone acetate is usually equally effective but hepatic conversion to active cortisol may be unpredictable in some patients. Prednisolone is used for some to attenuate the pronounced rise in precursor steroid concentrations which occur during the night time hours.

When statural growth is complete, dexamethasone is an effective form of treatment to use in the long term. The longer biological half life (about three and a half hours) allows medication to be administered only once,[12] or at the most, twice daily. Single daily medication should probably be given in the morning in a maximum dosage of 0·01 mg/kg/day or about 0·25–0·5 mg/day. The individual dosage requirement to achieve adequate control in congenital adrenal hyperplasia can be quite variable. Certainly the potency of dexamethasone relative to cortisol is about 80:1 rather than the figure of 30:1 quoted in standard texts. Treatment with dexamethasone is particularly effective in regulating menses and ensuring ovulation in postmenarchal women with congenital adrenal hyperplasia.[13] Other less conventional forms of medical treatment for congenital adrenal hyperplasia include the use of cyproterone acetate to block the tissue action of androgens and long acting analogues of luteinising hormone releasing hormone, to slow down puberty in patients who have an advanced bone age.[14]

Most patients with 21-hydroxylase deficiency are probably salt losers if a sensitive index such as plasma renin activity is used to assess mineralocorti-

coid secretion.[15] A previous annotation in this journal recommended that mineralocorticoid replacement could be discontinued for salt losing infants in later childhood.[16] The practice is potentially dangerous as any reduction in an acquired high salt intake can precipitate an adrenal crisis. Mineralocorticoid replacement should continue as 9α-fludrocortisone in a daily dosage of 0·1–0·15 mg. When adequate mineralocorticoid treatment is given, improved linear growth often occurs.[17] The principles of glucocorticoid replacement in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency are the same. Suppression of the increased concentration of deoxycorticosterone, a potent mineralocorticoid, sometimes precipitates a salt losing crisis.

How should control be monitored?

Clinical parameters of control in congenital adrenal hyperplasia include measurement of growth velocity and skeletal maturation (bone age), signs of hypercortisolism (striae, weight gain, hypertension), and noting the pattern of menses in postpubertal women. These are essential to monitor regularly but the parameters are insensitive indicators of control in the short term and are of necessity retrospective. Assessment of skeletal maturity is unreliable during infancy at a time when satisfactory control is essential if normal growth is to be sustained throughout childhood and adolescence. The outcome for adult height in the first generation of patients treated regularly with glucocorticoid replacement has generally been unsatisfactory.[18 19] Irregular menses and infertility in both sexes have been additional problems.

Several steroid parameters have been used to monitor adequacy of treatment in congenital adrenal hyperplasia. Urinary 17-oxosteroid and pregnanetriol excretion is an insensitive index of control and is seldom used now. Single random determinations of plasma 17OH-progesterone concentrations are difficult to interprete because of the combined influences of stress, an intrinsic circadian rhythm, and the timing of previous glucocorticoid medication on adrenal steroid hormone concentrations. A very high early morning concentration of 17OH-progesterone can fall to normal values by late afternoon even in a poorly controlled patient. The interpretation of a single estimation of 17OH-progesterone would clearly be quite different for samples collected in morning and afternoon clinics. The problem can be circumvented by the use of daily profiles of 17OH-progesterone. The availability to measure this steroid in filter paper blood spots and saliva makes it possible for frequent, serial

samples to be collected at home by patients with congenital adrenal hyperplasia of all ages.

Pictorial nomograms of 170H-progesterone rhythms have recently been constructed to interpret the daily profiles of blood spot and saliva 170H-progesterone measurements in individual patients with congenital adrenal hyperplasia.[20] The magnitude of the circadian rhythm is an important index of control. The disappearance of the rhythm is an early sign of overtreatment. Table 4 contains examples of profiles typical of various categories of control in congenital adrenal hyperplasia. Plasma testosterone measurement is also a useful marker of control and can be used singly as the concentrations do not fluctuate as widely as 170H-progesterone. If daily 170H-progesterone profiles are not used, then a single plasma measurement of this steroid and testosterone at 0800 hours is often informative. Adequate control is indicated by 170H-progesterone concentration in the range of 30–70 nmol/l in blood, 260–1000 pmol/l in saliva, and plasma testosterone concentrations <0·5 nmol/l (prepubertal children) and between 1·0–2·5 nmol/l (pubertal females). Measurement of plasma testosterone is of no value in the pubertal male due to the increasing contribution of testosterone from the testis which occurs at this age. Androstenedione is also an index of adrenal androgen secretion and is an alternative marker to monitor control in congenital adrenal hyperplasia.[21 22]

Measurement of plasma electrolytes is an insensitive index of mineralocorticoid replacement in congenital adrenal hyperplasia. Sufficient mineralocorticoid should be prescribed to maintain levels of plasma renin activity within a range appropriate for age. This applies particularly during infancy when concentrations up to 20 pmol/ml/hour are observed for normal infants. Measurement of plasma 11-deoxycortisol and testosterone are indices of control in congenital adrenal hyperplasia due to 11β-hydroxylase deficiency.

Prenatal diagnosis and treatment

Considerable information has been gathered on the genetics of congenital adrenal hyperplasia in recent years and the interested reader is referred to two excellent reviews of the subject.[23 24] Measurement of the concentration of 170H-progesterone in amniotic fluid collected during the second trimester of pregnancy is a reliable test for the prenatal diagnosis of 21-hydroxylase deficiency.[25] However, this is too late to prevent virilisation of an affected female by giving oral dexamethasone to the mother. HLA typing of amniotic cells can also be used for prenatal diagnosis but the method is technically more complex and the result may be misleading.

Table 4 *Typical daily profiles of 170H-progesterone in congenital adrenal hyperplasia related to degree of control*

Time (hours)	Undertreated		Adequately treated		Overtreated	
	Blood	Saliva	Blood	Saliva	Blood	Saliva
0800	70–240	6000	30–70	1000	<10	500
1200	15–140	4000	<15	500	<5	<150
1800	10–100	2500	<10	200	<5	<150
2200	10–20	2000	<10	150	<1	<150

The values given are only guidelines. Concentrations of 170H-progesterone in blood are in nmol/l and in saliva in pmol/l, respectively.

Analysis of a chorionic villus biopsy using DNA restriction fragment length polymorphisms would allow earlier prenatal diagnosis. The current cDNA probes for the 21-hydroxylase gene, however, show homozygous deletions in only a minority of patients with congenital adrenal hyperplasia. The analysis does allow for earlier fetal karyotype determination which will affect the need for prenatal treatment. One option in the 'at risk' pregnancy is to start maternal dexamethasone treatment (0·5–1·0 mg daily) empirically as early as 5 weeks' gestation and discontinue treatment for 10 days before an amniocentesis is performed at 16 weeks for steroid estimation. Treatment can be restarted if the concentration of 170H-progesterone is raised and the fetus is female. There are only isolated reports of the success of this treatment. Generally, there is a reduction, but not a complete absence, in virilisation of the female external genitalia.

Newborn screening

The incidence of congenital adrenal hyperplasia based on several pilot newborn screening programmes is about 1 in 10 000 white births, but as high as 1 in 230 among the Yupik Eskimos. Measurement of 170H-progesterone in a filter paper blood spot sample is simple to perform. However, false positive results are sometimes observed in sick preterm infants. Table 5 lists the problems which are

Table 5 *Problems potentially avoidable with newborn screening for congenital adrenal hyperplasia*

Salt wasting crisis
Inappropriate diagnosis and treatment of 'pyloric stenosis'
Inappropriate gender assignment
Precocious puberty
Stunted growth
Sudden death

potentially avoidable if screening for congenital adrenal hyperplasia was practised routinely. Even so, the incidence of cases that would not be detected clinically must be very low. A retrospective survey of a large number of patients with congenital adrenal hyperplasia in Birmingham showed an improvement in early diagnosis in children born after 1970.[26] The authors concluded that in countries like the United Kingdom, where a rapid 17OH-progesterone measurement is readily available, neonatal screening for congenital adrenal hyperplasia was not necessary.

Conclusion

Congenital adrenal hyperplasia is an uncommon chronic disorder which will present in the newborn nursery only about once every two years even in the busiest maternity unit. A high clinical index of suspicion should be maintained for all infants with abnormal genitalia and boys who fail to thrive. The diagnostic tests are readily available and reliable. Treated patients should expect a normal life span and reproductive potential. This can be achieved by careful attention to regular measurements of clinical parameters of control and supplemented with the use of more modern and sensitive biochemical indices of control.

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