Annotation

Archives of Disease in Childhood, 1974, **49**, 1.

Congenital adrenal hyperplasia

Congenital virilizing adrenal hyperplasia (sometimes known as the adreno-genital syndrome) is caused by a defect in the biosynthesis of cortisol as a result of deficiency in one of the essential enzymes, most commonly 21-hydroxylase.

The effect of the enzyme deficiency is a reduction in the secretion of cortisol. The plasma level falls and by a negative feedback mechanism there is a compensatory rise in ACTH secretion. The resulting over-stimulation of the suprarenal cortex causes an excessive production of androgens with consequent virilization.

In the fetus, this is the cause of the incomplete differentiation of the external genitalia in the female and, after birth, of the progressive virilization in both sexes, together with rapid growth and advance in development of the epiphyses—leading eventually to premature fusion and stunted growth.

In about one-third of patients with 21-hydroxylase deficiency a severe salt-losing syndrome develops soon after birth, which if untreated may prove fatal.

The aims of treatment are to prevent progressive virilization and to ensure normal growth and skeletal development.

These can be attained by the administration of a glucocorticoid that suppresses the high ACTH secretion, and thus reduces the over-stimulation of the suprarenal cortex. The plasma androgen level falls and this is reflected by the normalization of the excretion of urinary 17-ketosteroids, and the fall in the urinary pregnanetriol to normal levels.

Cortisone acetate was the steroid originally used by Wilkins *et al.* (1950). Hydrocortisone (Cortisol), being the hormone secreted by the adrenal, seems more physiological and is tending to displace cortisone in therapy. Zürbrugg (1969) claims that he has better results with hydrocortisone than with cortisone. As cortisone has to be metabolized to hydrocortisone *in vivo*, the suppressive dose of the latter may be lower than that of cortisone.

Because of their short life (6 to 8 hours), cortisone and hydrocortisone have to be given three times daily. Atherden, Barnes, and Grant (1972) have shown that in congenital adrenal hyperplasia the circadian rhythm persists, and that high early morning levels of 17-hydroxyprogesterone occur due to the high nocturnal secretion of ACTH, which is difficult to suppress completely by short-acting steroids. The last dose should be given as late as possible, just before bedtime, and in infants it may be administered at the 10.00 p.m. feed.

Migeon (1968) published a table of oral cortisone doses based on cortisol production rates. The daily dose should be from 2 to 3 times the cortisol secretion rate (12 to 36 mg/m^2 daily). This is similar to that suggested by Laron and Pertzelan (1968), namely 10 to 30 mg/m^2 daily.

To induce suppression of ACTH, about twice the above dose is given for 7 to 10 days, by which time the urinary 17-ketosteroid excretion should be normal. The dose is then quickly reduced to the appropriate maintenance level.

Other steroids having more prolonged suppressive effects have been employed in treatment, e.g. prednisone, betamethasone, dexamethasone, triamcinolone, etc. These, unfortunately, have a greater growth-suppressing effect than cortisone and hydrocortisone (Van Metre, Niermann, and Rosen, 1960; Laron and Pertzelan, 1968).

On page 4 of this issue, Bailey and Komrower (1974) report significant stunting and delayed skeletal maturation in 20 salt-losing patients, 14 of whom were treated in infancy with a long-acting glucocorticoid, prednisone trimethyl acetate, intramuscularly at 3 to 5 week intervals. Adequate control was achieved by these doses. 1 mg prednisone trimethyl acetate is equivalent to 5 mg hydrocortisone.

The majority of the children received the equivalent of 10 to 20 mg hydrocortisone/m^2 daily. After the age of 1 year the children were given oral prednisone in a dose equivalent to 10 to 30 mg hydrocortisone/m^2 daily. The author found, surprisingly, that prednisone trimethyl acetate did not influence the rate of growth during the first year of life, though subsequent oral prednisone therapy led to stunted growth that was thought to be due to overdosage. Nevertheless, in view of the known stunting effect of prednisone in early life, prednisone

trimethyl acetate treatment is not to be recommended as routine therapy in infancy.

Treatment should be monitored by regular estimations (3-monthly in infants, 6-monthly in older children) of the total urinary 17-ketosteroids, which should be within the normal range for the patient's age (Prout and Snaith, 1958). To obtain a satisfactory 24-hour urine collection the infants should be admitted to hospital for 48 hours.

If the 17-ketosteroid excretion is normal, it is not usually necessary to measure urinary pregnanetriol (normal values: under 6 years 0–0·2 mg/24 hours, 6 to 16 years 0·3–1·1 mg/24 hours).

Measurement of plasma 17-hydroxyprogesterone, the precursor of pregnanetriol, is sometimes useful, but should not be relied on for diagnosis. The level varies with the degree of suppression and even in treated cases may rise during the early hours of the morning. A high daytime level would be an indication that the patient is under-suppressed.

Under-treatment is evidenced by excessive growth and an undue increase in bone age. The urinary 17-ketosteroid excretion is high.

Over-treatment causes a slowing down of linear growth and retardation of bone age; the level of urinary 17-ketosteroids is below normal for the age.

The dosage must be manipulated to avoid these two extremes so that the patient grows at a normal rate and his bone age advances in proportion to age.

Within the last few years there have appeared a number of reports of retarded growth in treated patients, especially in the first 2 years of life (Bergstrand, 1966; Rappaport, Cornu, and Royer, 1968; Sperling *et al.*, 1971; Hamilton and Moodie, 1970).

Rappaport *et al.*'s 16 patients (all of whom were salt-losers) had severe growth retardation, greatest in the first year of life. Sperling *et al.* (1971) reported that 76% of their patients were below the 3rd centile.

Raiti and Newns (1971), on the other hand, found that only 8 of 35 salt-losers were below the 3rd centile. These patients were considered to have been given excessive doses of glucocorticoids.

A recent report on linear growth rate and bone maturation in congenital adrenal hyperplasia has been published by Rappaport *et al.* (1973). This study was designed to evaluate the effect of various oral hydrocortisone doses on linear growth and bone maturation. A normal growth rate was achieved with doses between 15 and 36 mg/m^2 daily and a reduced growth rate with doses between 27 and 55 mg/m^2 daily. The same range of doses was found when bone maturation was considered separately. There is, therefore, some overlap, but it appears from this study that the dose should be kept below 30 mg/m^2 daily if stunting is to be avoided.

Growth retardation occurs almost exclusively in the salt-losers, and is greatest during the rapid growth period in infancy. It appears to be related to excessive dosage during and after periods of infection. After infections, the dose should, therefore, be quickly reduced to the maintenance level.

Administration of glucocorticoids should be continued throughout life as the fundamental defect in cortisol synthesis persists. Once growth has stopped one of the long-acting steroids such as prednisone may be substituted. These have the advantage that they need be given only twice daily.

In males spermatogenesis is not proven to be impaired. In some adolescent females menstruation may be delayed or the menses may be scanty and infrequent. This may be due to inadequate suppression of ACTH, with a rise in plasma testosterone that may inhibit gonadotrophin release. Hayek, Crawford, and Bode (1971) found that a single dose (0·5 mg) of dexamethasone administered at midnight lowered the urinary 17-ketosteroid excretion to normal levels and the patient so treated menstruated after a long period of amenorrhoea.

The hormonal status of the adolescent female has not been adequately studied and more research is needed to determine why breast development and menstruation are delayed in these patients. Nevertheless, they are usually fertile and there have been many reports of mothers giving birth to normal babies.

Treatment of the salt-losing syndrome

Emergency treatment. Severe salt-losers present in the early weeks of life and may develop severe dehydration and circulatory collapse within 24 hours of the onset of vomiting. They must be regarded as medical emergencies.

Isotonic saline should be administered immediately. 25% of the total calculated volume for 24 hours should be given in the first two to three hours.

Deoxycorticosterone acetate (DOCA) 2 to 5 mg should be given in twice-daily doses. The electrolytes should be measured frequently and the above treatment continued until the serum sodium and potassium have reached normal levels.

Circulatory collapse should be counteracted by either intramuscular injection of 100 mg hydrocortisone twice daily or intravenous injection of hydrocortisone hemisuccinate in a dose of up to 10 mg/kg several times daily. There is little danger of overdosage during the emergency period.

After the infant is rehydrated and the serum electrolytes are normal, suppressive glucocorticoid therapy should be started and the DOCA gradually discontinued. Oral sodium chloride 3 to 6 g/day should be given.

Maintenance treatment. There are various ways of administering mineralocorticoids. DOCA in 125 mg pellets (2–4) may be implanted below the skin of the scapula. Each pellet is approximately equivalent to 0·5 mg of intramuscular DOCA daily. They will need to be replaced when the pellets can no longer be palpated.

DOCA may also be administered as a depot preparation (Percorten). The dose is 25 to 50 mg every 2 to 4 weeks, depending on the severity of the salt loss.

Another powerful salt-retaining steroid is 9α-fluoro-hydrocortisone (Florinef). The usual dose is 0·1 mg/day in two divided doses. Larger doses may be necessary but carry the risk of the development of hypertension. This has also been reported in some patients receiving Percorten. The blood pressure must, therefore, be measured frequently in patients treated with these steroids.

Even when patients are receiving mineralocorticoids a salt-losing crisis may be precipitated by an infection, injury, or surgical operation, and requires urgent treatment.

Most salt-losers can stop taking salt-retaining hormones at 4 to 5 years of age. Added salt may also be stopped early; the child will take more salt with his food. The explanation of the ability to do without salt-retaining hormone is not known since the defect in aldosterone synthesis persists.

Nevertheless, even in late childhood a salt-losing crisis may develop requiring emergency treatment; in such cases it is advisable to reinstate treatment with small doses of salt-retaining hormone.

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G. H. NEWNS
Institute of Child Health,
30 Guilford Street, London WC1N 1EH.