CONGENITAL ADRENAL HYPERPLASIA

REPORT OF A CASE IN A MALE INFANT

B. ZILBERG, M.B., CH.B., M.R.C.P.E., D.C.H.

Cape Town

Congenital adrenal hyperplasia is a rare cause of vomiting in infancy. In 1940 Wilkins, Fleischman and Howard[1] published the first report of this condition, in a male child. Despite the paucity of reported cases, it is commoner than is generally realized. Probably many cases are incorrectly diagnosed on account of the confusing clinical picture.

The adrenal cortex produces 3 types of hormone, and hyperadrenocorticism may result in over-production of any one of them. As a result, 3 distinct clinical syndromes may be attributed to adrenocortical overactivity:

1. *The adrenogenital syndrome* is due primarily to hypersecretion of the androgenic hormones and may be either congenital or acquired. The congenital variety is almost invariably the result of adrenal hyperplasia. When it occurs in the female it leads to varying degrees of pseudo-hermaphrodism (female intersexuality) with progressive virilization. In the male it leads to macrogenitosomia praecox. The condition is characterized by an excessive secretion of 17-ketosteroids and, in a considerable percentage of cases, this is accompanied by a deficient secretion of glucocorticoids and mineralocorticoids. When the hyperplasia arises postnatally, virilism results in the female and precocious sexual development in the male.

2. *Cushing's syndrome* is due to an excess of the glucocorticoids and is characterized by obesity of the 'buffalo' type, plethora and purple cutaneous striae, hypertension, hyperglycaemia, and occasionally osteoporosis.

3. *Primary aldosteronism or Conn's syndrome* has recently been recognized and is attributed to an excess of adrenal mineralocorticoids. It is characterized by intermittent muscular pains, cramps, weakness, paralyses and hypertension. Renal dysfunction occurs and tetany may be a feature. The blood shows hypokalaemia, hypernatraemia and alkalosis.

THE CLINICAL PICTURE IN CONGENITAL ADRENAL HYPERPLASIA

The clinical picture is due to an excessive secretion of androgens, modified in many cases by associated glucocorticoid and mineralocorticoid deficiency.

Effects of Excessive Androgen Secretion

In the female infant genital abnormality is recognizable from birth. There is usually enlargement of the clitoris. In severe forms the masculinization is more marked, with labio-scrotal folds and the persistence of a urogenital sinus which receives both urethra and vagina. Thus, in an infant with equivocal sex, congenital adrenal hyperplasia must be considered. Precocious development takes place in a male direction.

In the male excessive genital development may be present at birth, but is usually not noticeable till after 1 year of age. Sexual development progresses rapidly and the penis and prostate may attain adult size at an early age. Erections are frequent, sexual hair and acne appear prematurely, and the voice becomes deep. In spite of the marked development of secondary sexual characteristics, it is noteworthy that the testes usually remain small and immature and spermatogenesis does not occur. The patients, unless they succumb during crises, grow rapidly and become exceedingly muscular. Bone growth is accelerated and epiphyseal fusion occurs early. Thus growth stops prematurely and the child may present the picture of an 'infant Hercules'.

Effects of Glucocorticoid and Mineralocorticoid Deficiency

In many cases (Russell[2] reports 68% in a series of 38 males with congenital adrenal hyperplasia) evidence of mineralocorticoid and glucocorticoid deficiency of the type seen in Addison's disease becomes manifest within the first few weeks of life. The predominant symptom is vomiting, which may be projectile and may closely simulate that seen in pyloric stenosis. Dehydration soon follows, but death may occur before this becomes marked. Other features are diarrhoea, rapid breathing, and episodes of collapse with pallor or cyanosis. Frequently dehydration is out of keeping with the extent of vomiting or diarrhoea. A craving for salt may be a notable feature. The severity of these symptoms is variable. The severest forms simulate 'Addisonian crises' and, unless correctly treated, these crises may soon result in death.

The early recognition of this disease is important, for these patients can lead fairly normal lives if they receive adequate treatment.

Biochemical changes may not be present until the third week or may be found only during periods of crisis. The levels of serum sodium, chloride and bicarbonate fall, while that of serum potassium rises—a chemical picture like that seen in Addison's disease. The diagnosis may be confirmed by demonstration of the excessive urinary excretion of 17-ketosteroids and pregnanediol.

The family history may help in the diagnosis in that siblings are commonly affected or may have exhibited intersexuality.

THE UNDERLYING METABOLIC DEFECT AND ITS BIOLOGICAL EFFECT

In the normal individual the adrenal cortex is under the control of the anterior pituitary *via* its ACTH secretion. ACTH stimulates the adrenal cortex to secrete hydrocortisone and androgens. (The role of the pituitary gland in the control of aldosterone production has not been clearly elucidated.) Circulating hydrocortisone has an

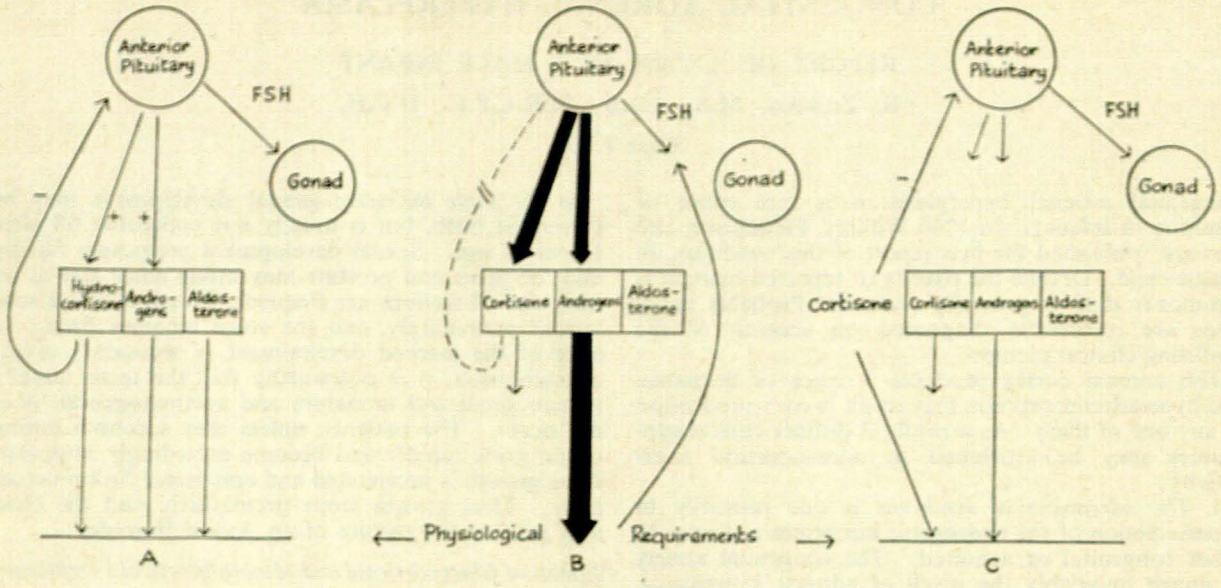

Fig. 1

(*a*) *Pituitary adrenal axis in normal individual.* The anterior pituitary *via* ACTH stimulates the adrenal cortex to secrete hydrocortisone and androgens. The circulating hydrocortisone has an inhibitory effect on the pituitary so that a homeostatic balance is established. *Via* FSH secretion gonadal maturation is stimulated.

(*b*) *Pituitary adrenal axis in congenital adrenal hyperplasia.* Owing to the deficiency of hydrocortisone synthesis, ACTH production is excessive, resulting in over-stimulation of the adrenal cortex, which pours out androgens. FSH is inhibited by the excess of androgens.

(*c*) *The effect of the administration of cortisone in congenital adrenal hyperplasia.* The cortisol deficiency is corrected and inhibition of ACTH production is effected. The adrenal is put to rest and the excessive androgen production is stopped. The 'brake' on FSH is removed, allowing gonadal maturation.

inhibitory effect on the anterior pituitary so that a fine homeostatic balance is established. *Via* FSH production the pituitary is responsible also for gonadal maturation (Fig. 1*a*).

The underlying defect in congenital adrenal hyperplasia is illustrated in Fig. 2. In the course of production of 17-hydroxycorticosterone (compound F, hydro-

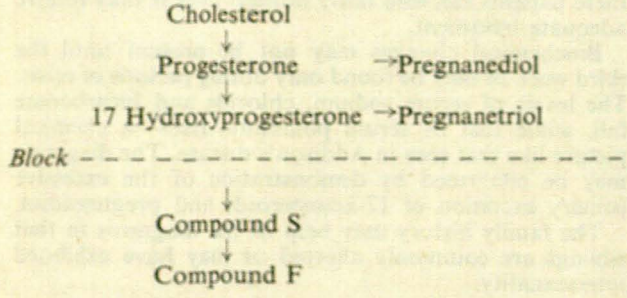

Fig. 2

cortisone or cortisol) by the normal adrenal, the last step involves the conversion of 17-hydroxyprogesterone to compound F.[3] Jailer[4] suggests that in congenital adrenal hyperplasia there is an enzyme block at the 17-hydroxyprogesterone stage with consequent excessive accumulation of this compound, which is reflected in the high levels of urinary steroids.

Thus hydrocortisone precursors accumulate, but there is an absolute deficiency of hydrocortisone itself. This results in uninhibited secretion of ACTH by the anterior pituitary. In its turn this causes the adrenals to hypertrophy and to secrete large quantities of androgens (Fig. 1*b*). In addition, ACTH excess leads to further over-production of abnormal steroids by the adrenals. These abnormal steroids are believed to be androgenic, though conclusive proof of this androgenic activity is lacking.[5]

As a result of over-production of these androgenic substances during intra-uterine life, external genital abnormalities occur in the developing female foetus. If the anomaly arises before sexual differentiation is complete, masculinization of the genital tubercle and urogenital sinus results. The extent of this masculinization varies from case to case. The commonest anomaly of the external genitalia is hypertrophy of the clitoris with a urogenital sinus opening into the perineum (the vagina usually opening into the urethra) and hypertrophied labio-scrotal folds. The severest forms show almost complete external maculinization, but a penile urethra is very rare. The mildest cases demonstrate only hypertrophy of the clitoris.

In the male foetus the changes are less striking; prostatic and penile enlargement may ensue.

The continued excessive production of androgens throughout childhood is responsible for precocious sexual development in the male, and for increasing

virilism with early masculine puberty in the female. But this is not true precocity, since spermatogenesis or ovulation does not occur. This may result from inhibition of FSH production by the large amounts of circulating androgens (Fig. 2*b*).

The deficiency of hydrocortisone which occurs in congenital adrenal hyperplasia is responsible for the metabolic features. Renal tubular function is impaired in the absence of cortisol, with consequent disturbances of water, acid and base metabolism; a tendency to dehydration, acidosis and hyperkalaemia results.

The increased susceptibility and poor response to infection occurring in the syndrome are related to the deficient production of hydrocortisone.

Aldosterone deficiency has not finally been shown to occur in adrenal hyperplasia, but may in part be responsible for the low serum-sodium levels.

When cortisone is administered to patients suffering from the adrenogenital syndrome it has a twofold action: (1) It inhibits ACTH production by its direct action on the pituitary; (2) it provides cortisone for body cells, thereby decreasing the tissue demand for cortisone and thus indirectly inhibiting the production of ACTH. The production of large amounts of androgens is stopped and virilization ceases. The clitoris or penis regresses and, in the female, breast development may now occur at the normal time. The depressant effect of the excessive androgens on FSH production is removed, so that eventual sexual maturation may occur (Fig. 1*c*).

CASE REPORT

In May 1954 a 3-weeks-old infant was admitted to the Birmingham Children's Hospital with a story of projectile vomiting which started a few days after birth. There was no constipation. Pregnancy and labour had been normal. Family history was non-contributory

Physical examination revealed a well formed, rather hirsute, infant with mild peripheral cyanosis. Visible gastric peristalsis was present, but no pyloric tumour was palpable on repeated examinations. The external genitalia were within normal limits and no other abnormal findings were present. Vomiting persisted after admission to hospital.

Special Investigations

Urinary examination and routine examination of the blood revealed no abnormality. No pathogens were isolated from the stools.

Chemical analysis of the blood gave the following results: Serum Na 128 mEq./l., Cl 100 mEq./l., K 8·5 mEq./l., Ca 12 mg.% CO_2-combining power 40·7 vols.%. Blood urea 50 mg.%. Fasting blood-sugar 100 mg.%.

Twelve hours later the chemical results were as follows: Serum Na 130·5 mEq./l., Cl 110·6 mEq./l., K 10 mEq./l., CO_2-combining power 16·5 vols.%.

An electrocardiogram showed tall, peaked T waves in most leads, supporting the biochemical diagnosis of hyperkalaemia.

Course and Treatment

At this stage the patient's clinical condition deteriorated. He was drowsy and dehydrated, the limbs were hypotonic, and tendon reflexes could not be elicited. The pulse rate and rhythm were normal.

Intravenous fluids were started and intake and output balances were kept. M/6 solution of sodium lactate was used to overcome the acidosis. Cortisone unfortunately was not available at this stage; 2 mg. of desoxycorticosterone acetate (DCA) was given intramuscularly. Correction of acidosis and hyponatraemia tends to lower serum-potassium levels. But these levels were considered to be dangerously high in this infant and more specific potassium-lowering measures were instituted, as follows: (1) Rapid lowering of the potassium level was attempted by the intravenous administration of 10% dextrose solution (20 ml. per lb. body-weight). At the same time 5 units of insulin was given subcutaneously and 4 c.c. of a 10% solution of calcium gluconate intravenously. (2) In an effort to produce a more permanent lowering of the potassium level, 1,600 mg. of 'Rezonium A', a cation-exchange resin with selective action on the K^+ ion, was given by stomach tube at 8-hourly intervals.

The intravenous administration of 'Rezonium A' and DCA was continued for 4 days, and the patient's clinical condition was much improved; 'blood chemistry' was now within normal limits. The patient was placed on oral dried-milk feeds with 2 g. of salt added daily. DCA, 2 mg. daily, was continued.

Four days after cessation of intravenous fluids, vomiting and dehydration recurred. The results of chemical examination were then: Serum Na 130·5 mEq./l., Cl 107·1 mEq./l., K 11·6 mEq./l., CO_2-combining power 33·3 vols.%. Balance studies showed negative Na^+ and Cl^- balance despite DCA and additional salt.

The results of estimations of urinary 17-ketosteroid were now available; they showed values of 5 mg. and 3 mg. per 24 hours on 2 successive days. These high values confirmed the diagnosis of adrenal hyperplasia.

Intravenous therapy was started again and the original therapeutic regime was followed. In addition, 25 mg. of cortisone daily was given by intramuscular injection. When thirsty, the patient was offered normal saline, which he drank with relish. After 48 hours the clinical condition improved and the results of chemical examination of the blood were normal. Intravenous therapy was discontinued and dried-milk feeds with 3 g. of salt per day were given. In view of a constant tendency to acidosis, 1 g. of NaCl was later replaced by an equivalent amount of M/6 solution of sodium lactate. An attempt to withdraw the DCA resulted in dehydration; this necessitated correction with subcutaneous infusions and DCA substitution was therefore continued.

Gradually the additional salt and sodium lactate were removed from the feed. Cortisone, 6·5 mg. 6-hourly, was administered orally. DCA was replaced by the long-acting depot preparation Percorten 17 (Ciba) (50 mg. of the crystalline preparation) being given every 4 weeks. 17-Ketosteroid excretion was now maintained at less than 1 mg. per 24 hours.

The patient was discharged on a regime of oral cortisone and depot DCA. His mother was advised to add salt to his feed should vomiting recur. In view of the liability to crises, return to hospital was advised in the event of any infective illness.

The case was followed up for 18 months, at which time the patient appeared to be developing normally; the bone age and 17-ketosteroid excretion were within normal limits.

DISCUSSION OF DIAGNOSIS

In this child the early occurrence of vomiting and crises of collapse with dehydration associated with acidosis, hyperkalaemia and hyponatraemia, strongly suggested the diagnosis of congenital adrenal hyperplasia. This diagnosis was confirmed by the finding of 24-hour 17-ketosteroid excretions of 5 mg. and 3 mg. on two successive days, the normal value for this age being less than 0·6 mg. per day.[2]

Differential Diagnosis

Other conditions which had to be considered in this case were:

1. *Congenital hypertrophic pyloric stenosis.* This was excluded by the very early onset of vomiting, the normal bowel actions, the absence of a palpable tumour, and the normal barium meal. The biochemical disturbance in pyloric stenosis is usually that of alkalosis. Other forms of intestinal obstruction were excluded by the absence of constipation and by the barium studies.

2. *Hiatus hernia* was excluded by the type of vomiting, the absence of haematemesis, and the barium swallow.

3. *Renal abnormality*. There were no urinary symptoms; and the absence of a renal mass, the normal composition of the urine, and the relatively low blood-urea (50 mg.% in the presence of dehydration), argued against a renal abnormality as the cause of the acidosis and hyperkalaemia.

DISCUSSION OF TREATMENT

Treatment aims at suppressing excessive production of androgen, replacing the hormonal deficiencies, and maintaining normal electrolyte balance.

In 1950 it was shown by Wilkins *et al.*[6] that cortisone in congenital adrenal hyperplasia suppresses the excessive secretion of urinary 17-ketosteroids and biologically active androgens. It prevents the virilizing effects of the androgens and the accelerated growth and premature fusion of the epiphyses. It also has a slight sodium-retaining effect and thus also helps in correcting the disturbed electrolyte state. The dual action of cortisone, (1) as a replacement measure and (2) as a 'brake' on excessive production of ACTH by the anterior pituitary, is diagrammatically shown in Fig. 1*c*. Initial suppression of androgen is effected by intramuscular cortisone in a dosage, for infants, of 25 mg. daily. After 5-10 days this dosage may need readjustment. Oral dosage is usually 2-3 times as high.[7] Adequacy of dosage is gauged by maintenance of 17-ketosteroid excretions at levels roughly appropriate to the age of the child, and by radiological evidence that bone growth is proceeding at the normal rate. The requirement of cortisone may diminish after a while and it may be possible to decrease the frequency of administration. In some patients it may be advisable to give weekly injections of slightly larger doses of cortisone.[8]

Cortisone alone will not control the loss of sodium in all patients. When it does not, additional salt up to 7 g. daily is given. If balance is still not maintained DCA is added.

During infections the amounts of salt and DCA must be increased, and in some cases increased dosage of cortisone may also become necessary.

Compound B (corticosterone) has marked sodium-retaining properties, and this may well be the ideal corticoid to use in the patient who shows a marked tendency to lose salt.

Management during Crisis

Replenishment of the sodium deficit is accomplished by the intravenous route.

Before intravenous cortisone became available reliance was placed on aqueous extracts of adrenal gland, up to 20 ml. a day being given in the infusion. Intramuscular cortisone was started at the same time. The use of the recently available intravenous preparation of hydrocortisone may prove life saving.

In our patient the diagnosis was first made during a period of crisis. The serum-sodium levels, however, did not drop low enough to warrant the intravenous use of aqueous glandular extracts, with the attendant danger of pulmonary oedema.

Other Measures

The very high potassium levels may require more rapid lowering than is effected by cortisone. Immediate treatment of hyperkalaemia consists of the intravenous injection of 5% calcium gluconate (between 0·5 and 3·0 ml per lb. body-weight and of 10% dextrose (20 ml. per lb.), and the subcutaneous injection of 5 units of insulin. Insulin and dextrose, by stimulating glycogenesis, accelerate the migration of potassium from the plasma into the cells. Calcium antagonizes the toxic effect of potassium on the myocardium. The cation-exchange resins may prove a useful adjunct to potassium-lowering measures. These act by extracting 'unwanted' ions and replacing them by ions contained within the structure of the exchange substance. 'Rezonium A' has sodium occupying the exchange site and the K^+ ion is withdrawn from the blood and replaced by Na^+ when Resonium is used in states of hyperkalaemia. It is suspended in a mucilage and given by gastric tube. The suggested dose for an infant is 600 mg. per lb. per day, given in 3 divided doses. It may also be used as a retention enema. Regular biochemical control is essential when these measures are employed.

SUMMARY

A case is described of congenital adrenal hyperplasia in a 3-weeks-old male infant presenting with 'Addisonian' crises.

The characteristic combination was present of vomiting, hyperkalaemia, hyponatraemia, dehydration, acidosis and excessive androgen-production.

The severe metabolic disturbance was corrected by the use of cortisone and long-acting DCA.

An interesting feature was the craving for salt shown by the patient during periods of crisis.

The pathogenesis of the condition and the mode of action of cortisone in controlling its features are discussed.

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