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Adrenogenital Syndrome: Diagnostic and Therapeutic Problems

By

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Six patients are described whose adrenogenital syndrome due to partial 21-hydroxylase deficiency. Three girls of prepubertal age developed symptoms of virilization, two boys showed sighs of precocious macrogenitosomia, while a pubescent girl was, in addition to producing an excessive amount of androgens, extremely obese. Bone age was in all cases much in advance of chronological age.

Since the disturbance of steroid metabolism is due to the deficiency of hydrocortisone production and its consequence is an increase in the amount of androgen metabolites, the obvious therapy is a substitution treatment. The side effects of corticosteroid treatment and in the given cases the existing obesity raise, however, a number of therapeutic problems. A successful therapeutic result can be achieved only if each case is judged in the reflection of the endogenous and exogenous environment and the therapy must be prescribed after a careful evaluation of the clinical and laboratory data.

The common feature of congenital adrenal hyperplasia and its clinical and biochemical consequences is defect of hydrocortisone synthesis due to enzyme deficiency. This is followed by the increasing secretion of ACTH with a consequent hyperactivity of the adrenal cortex. The necessary amount of hydrocortisone can be ensured only by an excessive production of androgen metabolites which induce virilization and promote ossification.

The adrenogenital syndrome (AGS) induced by congenital adrenocortical hyperplasia has various forms according to the phase of hydrocortisone synthesis in which the deficiency of a given enzyme arises. A deficiency may occur in 21-hydroxylase (with or without salt loss), 11-hydroxylase and 3-beta-hydroxydehydrogenase, a deficiency of the first named enzyme being the most frequent anomaly.

The literature contains numerous reports dealing with the biochemical and genetic aspects of AGS [1, 2, 5, 16] so that the present study has been restricted to diagnostic and therapeutic problems.

MATERIAL AND METHODS

The material consisted of 6 children with actual or suspected AGS. Data regarding hormonal aspects are included in the case reports. As far as possible, not only the urinary output of 17-ketosteroids but also the corticoid and pregnanetriol fractions were determined accompanied by suppression by the administration of exogenous steroids. Suppression was effected in one case by intravenously inject-

ed prednisolone and in 5 cases by oral administration of prednisolone or dexamethasone. The effect of suppression was determined by analysing the urine collected in the last 24 hrs. The methods of FEHÉR et al. [4 to 10] were employed for the determination of 17-ketosteroids, their fractions and other steroid metabolites.

For abbreviations see Table I.

TABLE I

Abbreviations

17-KS	= 17-ketosteroids
Ktg	= ketogenic steroids
17-ketosteroid fractions:	
HOE	= 11-OH-etiocholanolone
HOA	= 11-OH-androsterone
HOAD	= 11-OH-androstenedione
OE	= 11-keto-etiocholanolone
DEA	= dehydroepiandrosterone
E	= etiocholanolone
A	= androsterone
17-corticosteroid fractions:	
THF	= tetrahydrocortisol
ATHF	= allotetrahydrocortisol
THE	= tetrahydrocortisone
11-deoxy	= 11-deoxy-17-OH-corticoids
Pregnanetriol fractions:	
11-OH-PT	= 11-OH-pregnanetriol
11-O-PT	= 11-keto-pregnanetriol
5 PT	= 5-pregnenetriol
PT	= pregnanetriol
APT	= allopregnanetriol
++	= strongly increased value
+	= increased value
±	= uppermost normal value
—	= low value with reference to age

CASE REPORTS

Case 1. Z. G., a female patient 6 years of age. Enlargement of the clitoris had been observed at the age of 2½ years (Fig. 1). Weight at admission was 22 kg (+4 kg); height, 127 cm (+ 6 cm). The results of laboratory tests were negative. Blood pressure fluctuated between 140/80 and 120/80 mm Hg. Development of the carpal bones was that of a 10 to 12-year-old child. Calcification and epiphyses were normal.

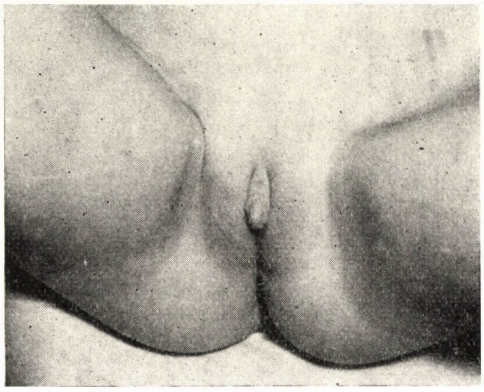

FIG. 1. External genitalia of 6-year-old girl (Case 1)

Daily urinary 17-KS output amounted to 27.0 mg, and 2 mg/kg of prednisolone failed to reduce it below 15.7 mg. Treatment with large doses of prednisolone caused the appearance of marked signs of Cushing's syndrome, so that the parents stopped further medication and refused to report subsequently despite repeated summons. Fig. 2 shows data collected during the three months of treatment.

Case 2. G. S., a girl, had first been admitted at the age of 2 years and 8 months. Enlargement of the clitoris had been noted at birth; growth of pubic hair had started at the age of 6 months and had become increasingly intensive from the age of 2 years. Weight at admission was 12 kg (— 1 kg); height, 93 cm (+ 2 cm);

blood pressure, 100/70 mm Hg. The size of the carpal bones was normal, their number was equal to that of 4 to 5-years-old children. The size of the carpal bones was normal, their number equal to that of 6 to 7-year-old children. The hydrocortisone level in plasma was below 5μg per 100 ml blood

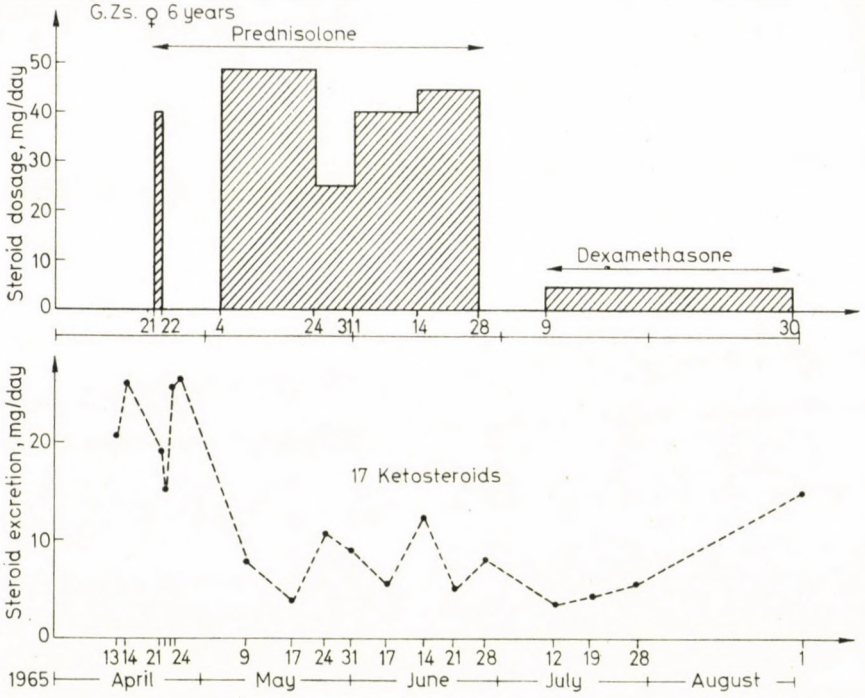

FIG. 2. Course of disease during 3-month observation (6-year-old girl, Case 1)

clitoris was about 2 cm, the labia majora were considerably enlarged; extensive pubic hair (Figs 3, 4). Increased urinary 17-KS and HOA output pointed to deficiency of 21-hydroxylation.

Treatment with decreasing doses of prednisolone (25, then 15, finally 10 mg daily) reduced the 17-KS level to a steady value of 1.5 to 1.3 mg/day (Fig. 5).

One year later her height was 95 cm; body weight, 13 kg; the size of the pressure was 105/65 mm Hg. Urinary 17-KS output was slightly above normal, while the previously pathological values of the androgen fractions were found to have dropped to the normal level. The clitoris was then amputated on account of cosmetic and psychologic considerations. With a maintenance prednisolone dosage of 10 mg daily, the child's 17-KS excretion is now, at the age of 6 years, in equilibrium (Table II), her face has become rounder and — no other symp-

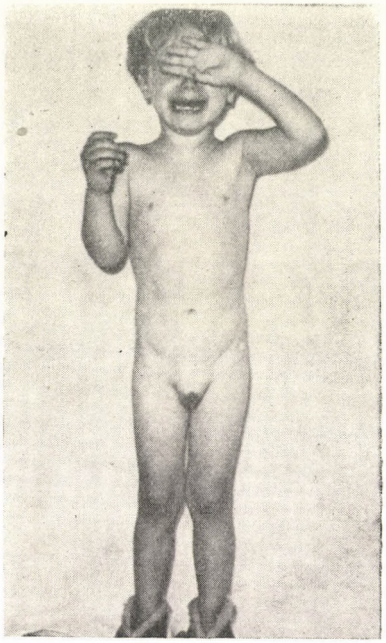

FIG. 3. Girl of 2 ½ years; partial 21-hydroxylase deficiency (Case 2)

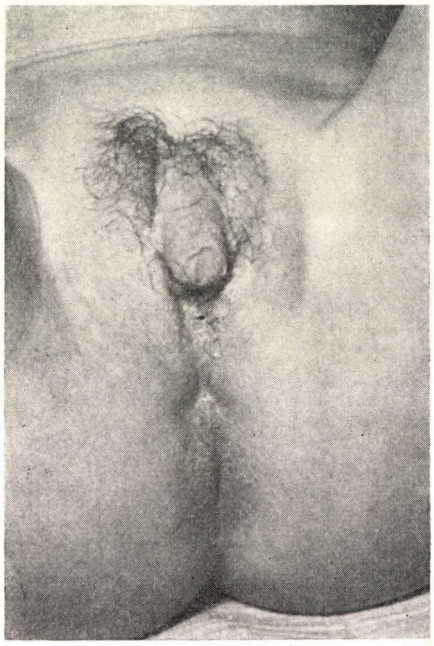

FIG. 4. External genitalia of 2 ½-year-old girl (Case 2)

toms of Cushing's syndrome are present. Blood pressure now is 125/80 mm Hg, body weight 15 kg, height 99 cm. These figures mean, referred to the average values at her age, a retardation of about one year.

Case 3. N. T., a female 7 month premature baby of a primipara was born with a weight of 900 g. Suspected of AGS on account of the size of the clitoris (Fig. 6), we examined the infant at the age of four months, when body weight was 3250 g; length, 51 cm; head-circumference, 41.5 cm. Ionogram, blood smears, ESR, electrophoretogram, urine analysis showed normal values. Number and size of carpal bones were those of a newborn. Data regarding urinary 17-KS fractions are listed in Table III. The high 17-KS and A values (0.7 mg) returned to normal (A dropped to 0.03 mg), and HOAD (which is not present under physiological condi-

TABLE II

Steroid excretion, Case 2

Steroid mg/day	Before	1 year after	3 years after
	prednisolone treatment		
17-KS	9.8++	3.2+	1.4
Ktg		3.8+	2.5
HOE	0.0	0.11	0.06
HOA	3.4++	0.10	0.04
OE	0.7+	0.17	0.10
DEA	0.0	0.0	0.0
E	0.5	0.08	0.04
A	0.0	0.07	0.0

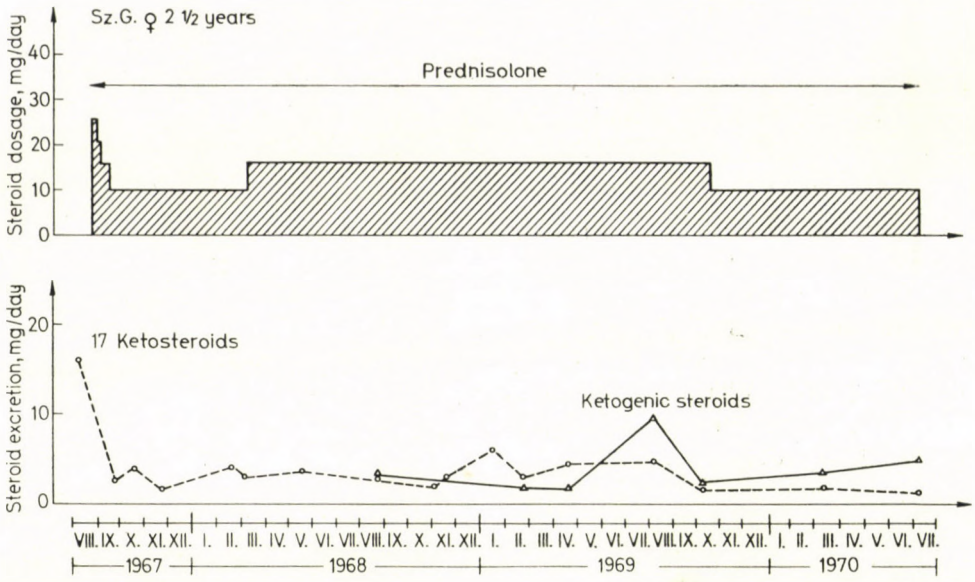

FIG. 5. Course of disease during 3 years of observation

tions) disappeared on prednisolone suppression. This pointed to a non-salt-losing type of 21-hydroxylase deficiency.

The child was re-examined at the age of 2½ years. Despite our previous advice, she received no steroid substitution. The child displayed an excellent somatic and mental development. The body weight of 11.6 kg and the height of 94 cm exceeded the mean for term children. The previously striking hypertrophy of the clitoris was markedly reduced (Fig. 7), but the bone age was 3½ to 4 years. Analysis of urinary steroids proved the existence of partial 21-hydroxylase deficiency (Table III).

Case 4. J. K., a boy of 6½ years, had shown signs of hypergenitalism

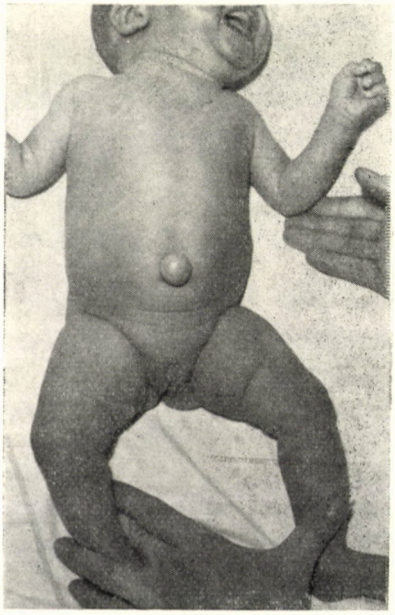

FIG. 6. External genitalia of 4-month-old girl (Case 3)

since the age of 3. His voice had become deep with 5 years. Body height at admission was 141 cm (+ 20 cm); weight, 34.5 (+ 11 kg); I.Q., 0.83; mental age, 5.4 years (retardation of about 13 months); slight imbecility. Laboratory tests were normal; blood pressure, 120/70 mm Hg; external genitalia like those of a 14 to 16-year-old boy (Figs 8, 9); anatomical and bone age, 12 years. Urine analysis (Table IV) revealed high 17-KS values, an increase of the individual androgen metabolites and

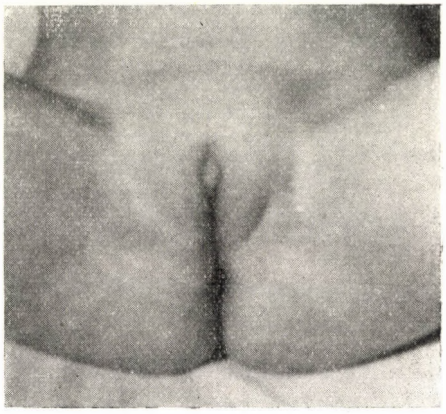

FIG. 7. External genitalia of girl in Fig. 6 at the age of 2 ½ years (Case 3)

TABLE III

Steroid excretion (Case 3)

Steroid mg/day	At the age of 4 months		At the age of 2 ½ years	
	Before	After	Before	After
	prednisolone suppression			
17-Ks	2.3 ++	0.5	2.2 ±	0.4
Ktg	1.3 ±	0.0	4.2 ±	0.7
HOE	0.0	0.02	0.06	trace
HOA	0.0	0.02	0.14 +	0.03
HOAD	0.7 ++!	0.0	0.0	0.0
OE	0.0	0.04	0.13 +	0.016
DEA	0.0	0.0	0.04	trace
E	0.0	0.03	0.06	0.01
A	0.7 ++	0.03	0.11 ++	0.016
THF	0.3		0.16	0.06
ATHF	0.6		0.13	0.04
THE	0.0		0.62	0.10
11-deoxy	0.3		0.17 ±	0.02
11-OH-PT			0.2 ++	
11-O-PT			0.05 ++	
5 PT			0.04 ++	
PT			0.07 +	
APT			0.0	

the presence of 11-OH-PT, 11-O-PT, phenomena which pointed to adrenocortical hyperplasia (blocked 21-hydroxylation). Steroid suppression reduced the steroid metabolism to normal (Table IV). Dexamethasone was prescribed, but the parents discontinued the treatment.

A follow-up examination at the age of 10 years revealed the neglect of medication.The previously diagnosed precocious macrogenitosomia was unchanged. Body weight, 48 kg (+ 20 kg); height, 163 cm (+ 23 cm); bone age 15—16 years; complete ossification of the epiphyses. Urine analysis showed the typical picture of untreated AGS (Table IV).

Case 5. I. T., a male child 12½ of years, born of a family of tall stature, had grown 8 cm in the year prior to admission. Pubic hair had begun to appear at the age of 11. The boy conveyed the impression of a robust young man of 16—18 years whose mental age was in excess of his chronological age (Fig. 10). His body weight was 90 kg (+ 40); height, 177 cm (+ 16 cm); blood pressure was varying from 130/80 to 160/80 mm Hg. The eyegrounds displayed somewhat tense arteries and normal papil-

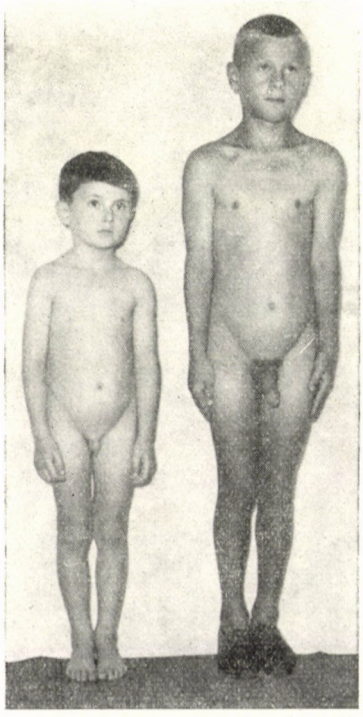

FIG. 8. Boy of 6 ½ years with precocious macrogenitosomia (Case 4) and normal boy of same age

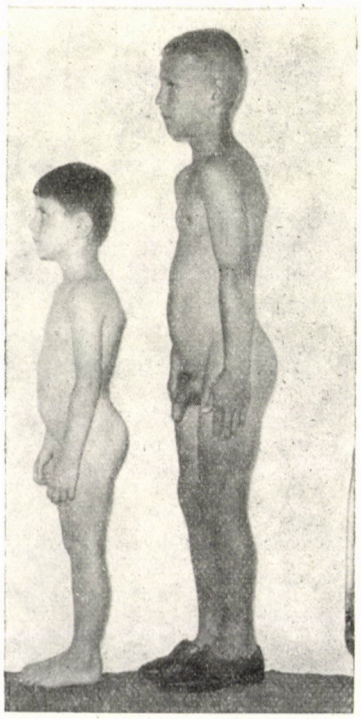

FIG. 9. Boy of 6 ½ years with precocious macrogenitosomia (Case 4) and normal boy of same age

lae. Bone age, 15—16 years. The results of laboratory tests were negative. The plasma hydrocortisone level varied between 12 and 30 μg per 100 ml. Urinary output of 17-KS (18.6 mg) and Ktg (3.4 mg) rose to

partial 21-hydroxylase deficiency. The appearance of PT fractions and the success of suppression therapy exclused the possibility of an adrenal tumour. The patient's obesity and moderate (though fluctuating) hyper-

TABLE IV

Steroid excretion (Case 4)

Streoid mg/day	At the age of 6 ½ years		At the age of 10 years	
	Before	After	Before	After
	dexamethasone suppression			
17-KS	41.0 ++	6.5	29.0 ++	7.2
Ktg	35.0 ++	8.7	36.5 ++	9.7
HOE	1.6 ++	0.0	1.3 ++	0.4
HOA	14.6 ++	1.7	7.0 ++	1.0
OE	3.8 ++	0.3	3.8 ++	0.7
DEA	1.6 ++	0.0	1.1 ++	0.4
E	3.2 ++	0.3	2.8 ++	1.3
A	6.5 ++	0.5	3.4 ++	1.1
THF	3.3 ++	0.7		
ATHF	0.0	0.0		
THE	11.3 ++	1.2		
11-deoxy	29.2 ++	2.2		
11-OH-PT	0.07 ++			
11-O-PT	0.05 ++			
5 PT	0.14 ++			
PT	0.16 ++			
APT	0.06 ++			
PT fractions total			10.3 ++	2.25 +

40 and 15 mg, respectively, after the oral administration of 3 g metyrapone. The concentration of HOA, DEA, A, 11-OH-PT and 11-O-PT showed pathological values (Table V). Hormone analysis and prednisolone suppression have made it evident that the precocious puberty was due to a tension contraindicated steroid substitution. The patient failed to report for a follow-up examination.

Case 6. E. D., an obese girl of 12 years, had had two menses at, and non since, the age of 10 years. Physical examination at admission revealed striae on the arms, shoulders

and thighs, further, acnes on the forehead, mild sprouting of a moustache and extensive hypertrichosis. Body weight, 90 kg (+ 50 kg); height, 162 cm (+ 10 cm); blood pressure, 160/100 to 170/110 mm Hg. Laboratory tests and intravenous pyelography showed normal conditions. The plasma hydrocortisone level was 36 μg per 100 ml. The results of urine analysis pointed to a deficient 21-hydroxylation.

At a follow-up examination at the age of 14 years (Fig. 11), body weight was 80 kg; height, 169 cm; bone age, 16 years, with complete ossification of the epiphyses; blood pressure, 140/90 mm Hg; normal uterus, free adnexa, hypoplastic labia minora, slightly undersized clitoris; hairs rather of the virile type; thin strip of hair between umbilicus and symphysis; marked hair growth around the breasts. Examined over a four-week period, vaginal smear cytology confirmed the diagnosis of hyperandrogenic amenorrhoea, as in the smear cells of the superficial and intermediary types were intermingled. The eosinophilic and pycnotic indices invariably remained below 10—20% during the four weeks of observation. Suppression by 8 mg dexamethasone daily for 3 days, together with the urinary hormone excretion seemed

FIG. 11. Girl of 14 years (Case 6) with adrenocortical hyperfunction

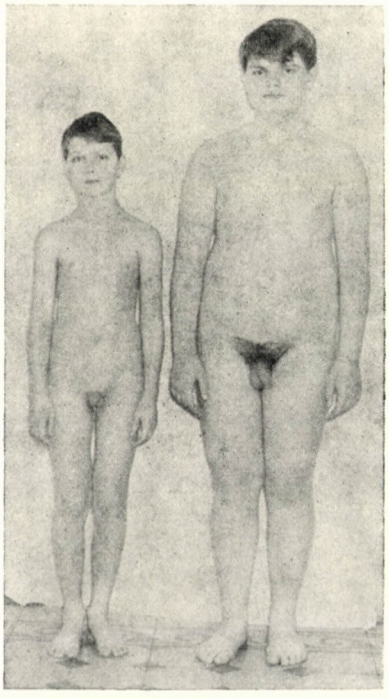

FIG. 10. Boy of 12 years with precocious macrogenitosomia (Case 5) and normal boy of same age

TABLE V

Steroid excretion (Case 5)

Steroid mg/day	Before prednisolone suppression	After prednisolone suppression	Before metyrapone load	After metyrapone load
17-KS	26.2 ++	5.1	18.6	40.0
Ktg	13.7 ++	3.2	3.4	15.0
HOE	0.9	0.4		
HOA	2.7 ++	0.7		
OE	1.8 ++	0.0		
DEA	2.7 ++	0.0		
E	5.2 ++	1.6		
A	13.2 ++	2.1		
THF	2.1 ++			
ATHF	1.0 ++			
THE	6.8 ++			
11-deoxy	0.7			
11-OH-PT	0.05 ++	0.05 ++		
11-O-PT	0.13 ++	0.10 ++		
5 PT	0.15 ++	0.06 ++		
PT	0.48 ++	0.18 ±		
APT	0.08 +	0.06 +		

to confirm a 21-hydroxylase deficiency (Table VI). Suppression resulted normalization of KS and PT values, and an elevation of the oestrogen level. Under the effect of dexamethasone the diurnal hydrocortisone level remained within physiological limits.

DISCUSSION

AGS, a recessively inheritable enzyme deficiency, represents a typical inborn error of metabolism. The frequency of the gene carrying the disease varies from population to population, the reason why there occurs one case of AGS per 5000 children according to PRADER [14], against a ratio of 1 : 67000, according to CHILDS [3]. It is worthy of note that HIRSCHFELD and FLESHMAN [13] found a 1 : 1500 ratio of salt-losing AGS among Alaskan Eskimos, a figure pointing to an extremely high gene frequency.

The diagnosis of AGS is facilitated by the symptoms of virilization and verified by the analysis of hormones excreted in urine. Urinary 17-KS output is above the normal level, but the subvariants of AGS can be de-

TABLE VI

Steroid excretion (Case 6)

Steroid mg/day	At the age of 12 years	At the age of 14 years	
		Before dexamethasone suppression	After
17-KS	20.4 ++	25.0 ++	6.4
Ktg	6.8 ++	23.5 ++	1.4
HOE	0.6	0.7	0.0
HOA	2.6 ++	2.6 ++	0.0
OE	1.4 ++	1.2 ±	0.0
DEA	0.0	3.7 ++	0.0
E	2.4 +	3.8 ++	0.2
A	2.4 +	6.3 ++	0.4
THF	0.0	0.5	0.0
ATHF	0.5	0.0	0.0
THE	4.1 +	2.1	1.5
11-deoxy	3.8 +	0.0	0.0
11-OH-PT		0.7 ++	trace
11-O-PT		0.18 ++	trace
5 PT		0.4 ++	trace
PT		1.8 ++	trace
APT		0.09 ++	0.0
Oestriol	6.4	5.4 —	6.9
Oestradiol	6.4	1.0 —	12.4
Oestrone	3.2	4.6 —	12.4
Plasma hydrocortisone, (μg/per 100 ml)	36.0	8 o'clock 23.5 17 o'clock 17.7	9.0

termined only by a careful analysis of the steroid fractions [5, 16].

Increased excretion of pregnanetriol derivatives (mainly metabolites of 17-alpha-hydroxyprogesterone) is a typical feature of 21-hydroxylase deficiency. While under physiological conditions about 0.2 mg of PT is excreted daily, several mg are eliminated by patients with AGS. Excretion of 11-OH steroids and androgens is likewise enhanced; HOAD may appear as a consequence of overproduction of adrenal androgens [5].

In 11-hydroxylase deficiency, the excretion of Reichstein's compound S (11-deoxycortisol), deoxycorticosterone and androgens are increased [5[

Excessive excretion of pregnenolone derivatives and DEA, further the

absence of 17-OH corticosteroids are of diagnostic value in cases of 3-beta-OH-dehydrogenase deficiency [5]. The suppression test is the most important differential diagnostic tool. Exogenous corticosteroids, if administered in adequate doses, diminish pituitary activity [5] and thus ACTH synthesis, so that the amount of the pathologic steroid fractions and, in particular, the excretion of 17-KS are reduced. Suppression cannot be achieved in the case of a tumour because then hormone secretion is independent of pituitary activity.

The diagnosis of partial 21-hydroxylase deficiency was verified in five of the above described six patients. Symptoms of virilization and advanced ossification were common features in all of them. Administration of exogenous steroid reduced the total 17-KS value to the normal level in all the five patients, excluding at the same time the presence of an adrenocortical tumour.

In Cases 3, 4 and 5, the PT fractions were also examined and the presence of PT derivatives, especially of 11-OH-PT and 11-O-PT characteristic of deficient 21-hydroxylation, was demonstrated.

Therapy

Since a relative hydrocortisone deficiency is present in all types of AGS, therapy must consist of the substitution of the deficient corticosteroid; this at the same time remedies the disturbance of metabolism through the feed-back mechanism. The dose of hydrocortisone to be prescribed is that smallest amount which maintains the excretion of 17-KS at the level corresponding to the patient's age. The usual dosage of prednisolone is, according to the literature, between 2.5 and 10 mg daily [1, 16]. This substitution therapy has to continue throughout life and must not be interrupted on account of intercurrent diseases. While it arrests further virilization, the existing anomalies are irreversible so that cosmetic surgery (e.g. amputation of the clitoris) may become necessary. Adjustment of steroid metabolism often restores normal menstruation [2] and even pregnancy may ensue [15].

Simple as the therapy appears to be, it may become difficult if the patient is obese (e.g. in our Cases 5 and 6) or if it provokes the symptoms of Cushing's syndrome (as in our Case 1). The situation may become still more difficult if the parents, failing to see the gravity of the disease (as in Cases 1, 3 and 4), disregard the physician's therapeutic instructions.

Recent attempts to combine prednisolone with certain competitive androgen antagonists [12] have been promising. Aminogluthethimide (Elipten R, Ciba), by inhibiting the activity of 20—22 desmolase (an enzyme involved in steroid biosynthesis at an early stage), decreases the production of androgens; consequently, premature ossification may be prevented and prednisolone in comparatively small doses may restore to normal the KS values.

Conclusions

Biochemistry of the adrenal cortex has ceased to be of mere theoretical significance in paediatric practice. Examination of the urinary excretion of steroids and their metabolites supplies information on the origin of enzymatic disorders responsible for adrenocortical hyperplasia, and helps in instituting the necessary treatment. This is of special importance in the highly dangerous salt-losing conditions.

Biochemical analysis has a differential diagnostic value: it enables the physician to differentiate between hyperplasia and tumour. According to recent observations, it is moreover possible to determine the degree of 21-hydroxylase deficiency by an ACTH load performed during substitution treatment. A deficiency of 80% or more is necessarily associated with a salt-losing syndrome [11].

The total 17-KS value indicates, at the most, the androgenic hyperactivity. The reliable diagnosis of suspected AGS requires the determination of individual urinary 17-KS, pregnanetriol and corticosteroid metabolites. Reliable biochemical diagnosis is only possible if the urinary output of physiological and pathological metabolites is known; the presence of the latter derivatives points to AGS even if the excretion of 17-KS is just slightly increased or normal. Since the opposite may also be true (as in our Case 6), pathologic laboratory data have to be reconciled with the clinical picture.

Although the biochemical background of AGS is always the same, i.e. an enzymatic inhibition of hydrocortisone production, the endogenous and exogenous milieu in which the loss of function occurs is nevertheless of significance. Of our 5 AGS patients it is only in a single case that substitution treatment is continuing smoothly. One of the children (Case 1) has been lost of sight. In Case 3, the excessive androgen synthesis caused by the slight 21-hydroxylase deficiency must have been favourable during the first two years of life both for the somatic and the motoric development of the prematurely born child. Although the result of urine analysis at the age of $2\frac{1}{2}$ years, and the advanced ossification proved the continued existence of virilization, the modest degree of androgen production and the absence of masculinization (growth of hairs) have made us to postpone substitution treatment for another year, until systematic control will become technically easier.

In Case 4 (macrogenitosomia) the prescribed treatment was discontinued by the parents. The external genital organs had undergone no change, and ossification had been completed in the 4 years between the first and the second hospitalization. Sexuality, becoming a central psychic problem, is a matter of anxiety in the case of this imbecile boy. No similar problem arose in connection with the other boy (Case 5) who, too, displayed all signs of the same anomaly so that no treatment was instituted.

In Case 6, menstrual disturbances, hirsutism and obesity were the predominant features, while the most typical signs of virilization (hyperplastic clitoris, athletic build) were absent. The increased total 17-KS, androgen- and PT fractions, pointed to a partial 21-hydroxylase deficiency (Table VI) which improved on dexamethasone suppression so that the possibility of an adrenocortical neoplasm was out of question. However, a careful examination of the case (Fig. 11) suggested the possibility of an incipient Cushing's syndrome, a generalized hyperactivity of the adrenal cortex which manifests itself with an increased excretion of total and individual 17-KS and PT, further, with obesity and hirsutism, while pronounced virilization, the typical symptom of AGS, is lacking. It is not clear why the low oestrogen values rose after suppression by dexamethasone. It is conceivable that androgens, synthesized in large amounts, acting as substrate inhibitors, prevent oestrogen production, a theory that has still to be confirmed.

Although, essentially, the non-salt-losing adrenogenital syndrome, induced by partial 21-hydroxylase deficiency, is based on a single biochemical mechanism, the therapy and the time of its commencement have to be adjusted to the actual conditions in each individual case and according to the evidence of all clinical symptoms and laboratory data.

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