DEFICIT OF 21 β-HYDROXILASE

Clinico-Functional Parameters

M. GANGEMI, M. BENATO,
A. M. GUACCI, G. MENEGHETTI

Institute of Gynecology and Obstetrics
University of Padua (Italy)

SUMMARY

The Authors report the hormonal pictures of 5 young women with partial deficit of 21-β-hydroxylase. They performed 17OH-progesterone, DHEA-S, plasma cortisol, free urinary cortisol, testosterone, ACTH and urinary 17KS assays. They then performed a suppression test by Desametazone and stimulus test by ACTH.

The Authors stress the major role of 17OH progesterone, assayed in basal conditions and after ACTH stimulus, recalling the importance of early diagnosis.

Authors also stress that in these patients testosterone is always significantly high.

INTRODUCTION

In puberty the adrenal glands undergo morphologic changes which mirror the stronger functional stimuli they must emit in this period of life. For instance, in women, the development of pubic and axillary hair is mainly stimulated by adrenal androgens. When the normal activity of adrenal enzymes is already intense, a higher functional demand may cause their exhaustion if a slight and therefore latent deficit pre-existed.

This is what usually happens with 21-β hydroxylase, the most frequent adrenal deficit. This enzyme, located on the pathway of both glycocorticoids and mineralcorticoids, allows 17 hydroxyprogesterone and progesterone to turn respectively into 11 desoxycortisol and desoxycorticosterone ([1, 2]).

This enzymatic deficit appears through two clinical syndromes:

a) the non salt-losing syndrome;
b) the salt-losing syndrome.

Both forms are characterized by evidence of virilization.

The a-form mainly concerns the gynecologist, as it appears rather late. It is a light form, mainly expressed by hirsutism with or without menstrual irregularities.

The b-form is the pediatrician's exclusive concern since it appears at birth through the typical character of female pseudohermaphroditism. It is extremely serious, because of its influence on electrolytes and blood pressure.

The resulting changes can rapidly be letal if the diagnosis is not established very early.

The pathogenesis of the non salt-losing form is positively ascribable to a deficit of the 21-β hydroxylase enzyme which is relevant in the glycocorticoid pathway (hence hypocortisolemia, ACTH hyperincretion and subsequent androgen overproduction).

Conversely, the pathogenesis of the salt-losing form is uncertain and several approaches have been tried to identify

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
X, n. 4, 1983

Table 1. — *Clinical data of 5 patients affected by 21β-hydroxylase deficit.*

Names	Reg. age	Bone age	Height	Weight	A.P.	Clinical sign.	+ Gyn. exam. Pathol. data	Instrumental tests	Interventions
C. N.	12	17	1.50	63	130/80	– amenorrhea – clitoridomeg. – hirsutism – muscular hypertrophy	– persistent urogen. sinus – hypoplastic uterus	– colpography	– plastics of urogen. sinus and external genitalia
C. S.	18	19	1.58	54	120/90	– regular menses – clitoridomeg. – hirsutism – breast hypoplasia	– hyperplasia labia majora – hypoplastic uterus	– laparoscopy	
F. L.	18	19	1.52	55	125/90	– polymenorrhea – hirsutism	– hypoplastic uterus	– laparoscopy – suprarenal CAT	
F. M.	10	17	1.48	48	125/70	– amenorrhea – clitoridomeg. – hirsutism	– coalescence labia minora – hypoplastic uterus	– laparoscopy – vaginoscopy	– nympholysis
P. P.	17	19	1.71	59	130/90	– regular menses – hirsutism	– hypoplastic uterus	– suprarenal CAT	

Table 2. — *Basal hormonal values (9 a.m.) in 5 patients affected by 21β-hydroxylase deficit.*

Cases	17 OH prog. ng/ml	DHEA-S pg/ml	Testosterone ng/ml	ACTH pg/ml	Cortisol g % 8 a.m.	Cortisol g % 8 p.m.	Free ur. cort.	17 KS mg/24 h
1 C.N.	75.0 *	2.9	3.2 *	200 *	31.5 *	10.8	170 *	63.0 *
2 C.S.	7.5 *	1.5	9.8 *	13	18.2	9.8	23	10.6
3 F.M.	4.0 *	2.8	10.8 *	91	14.0	9.9	50	7.0
4 F.L.	6.3 *	2.5	2.1 *	—	7.8	3.1	20	35.0 *
5 P.P.	10.0 *	3.1	4.9 *	111 *	15.4	6.1	332 *	31.4 *
N.V.	2	0.8-3.4	0.1-0.9	40-100	5-20		50-120	4-15

* Pathological levels; N.V. = normal values.

it ([3-9]). The deficit is transmitted as sex-independent recessive mendelian character ([10, 11]).

This study wants to review the clinico-functional parameters of this syndrome, in the framework of the etiologic differentiation of hirsutism, to offer gynecologists more useful diagnostic parameters.

MATERIAL AND METHODS

We examined 5 female patients affected by 21-β-hydroxylase deficit in the non salt-losing form. Table 1 shows the clinical data, the findings of the instrumental tests and the interventions performed on each patient.

Two patients presented primary amenorrhea at the time of the diagnosis whereas in the remaining 3 the menarcha had occurred between 10 and 12 years of age.

Assays were made of plasma ACTH, 17-hydroxyprogesterone, dehydroepiandrosterone, testosterone, cortisol (plus urinary free cortisol), FSH, LH, HPRL, 17-β-oestradiol on blood samples taken at 9 a.m., in basal conditions.

Furthermore the basal 17KS were assayed in the urine of 24 hrs.

Then, 3 patients underwent suppression test by Desametazone. The basal values were compared to the values obtained after suppression of free urinary cortisol, plasma cortisol, 17KS and 17-hydroxyprogesterone. This suppression test was performed with the administration of Decadron (0.5 mg × 4 per os) for 3 days.

We also measured the ACTH stimulus by assaying plasma cortisol, DHEA-S and 17-hydroxyprogesterone before and 1 hour after endovenous injection of Synacthen (0.25 mg) in bolus.

Table 2 shows the basal values of the individual hormones whereas tables 3 and 4 show respectively the figures concerning the suppression by Desametazone and the ACTH stimulus test. The following data are those concerning the hormonal assays that were performed.

ACTH: assay by kits (ACTHK CEA-IRE Sorin):
n.v. 40-100 pg/ml.

17OH-progesterone: RIA method. Mantero and Coll. methodology (unpublished):
n.v. in woman in follicular phase: 0.701.75 ng/ml;
n.v. in woman in luteal phase: 2.2-3.2 ng/ml.

DHEA-S: assay by EIRRIA kits:
n.v. prepuberal woman 0.27-1.54 mol/l;
n.v. adult woman 3.37-8.55 mol/l.

Plasma cortisol: assay by Premix kits:
n.v. A.M. 5-20 μg %;
n.v. P.M. approximately 1/2 of the value.

Testosterone: assay by Nordiclab kits:
n.v. 0.1-0.9 ng/ml.

Free urinary cortisol: assay by DPC RIA kits:
n.v. 50-100 μ %.

Urinary 17-ketosteroids: colorimetric assay by Zimmerman reaction:
n.v. 5-15 mg/24 hrs.

DISCUSSION

In the deficit of 21-β hydroxylase there is a lower production of cortisol and aldosterone, accumulation of 17 hydroxyprogesterone and, subsequently, of its metabolite pregnanetriol, androstenedione and testosterone.

In our cases the partial deficit of 21-β hydroxylase was not associated with signs of electrolytic imbalance related to the aldosterone deficit which appears always very early and can lead to death in the immediate post-natal period unless they are treated in time.

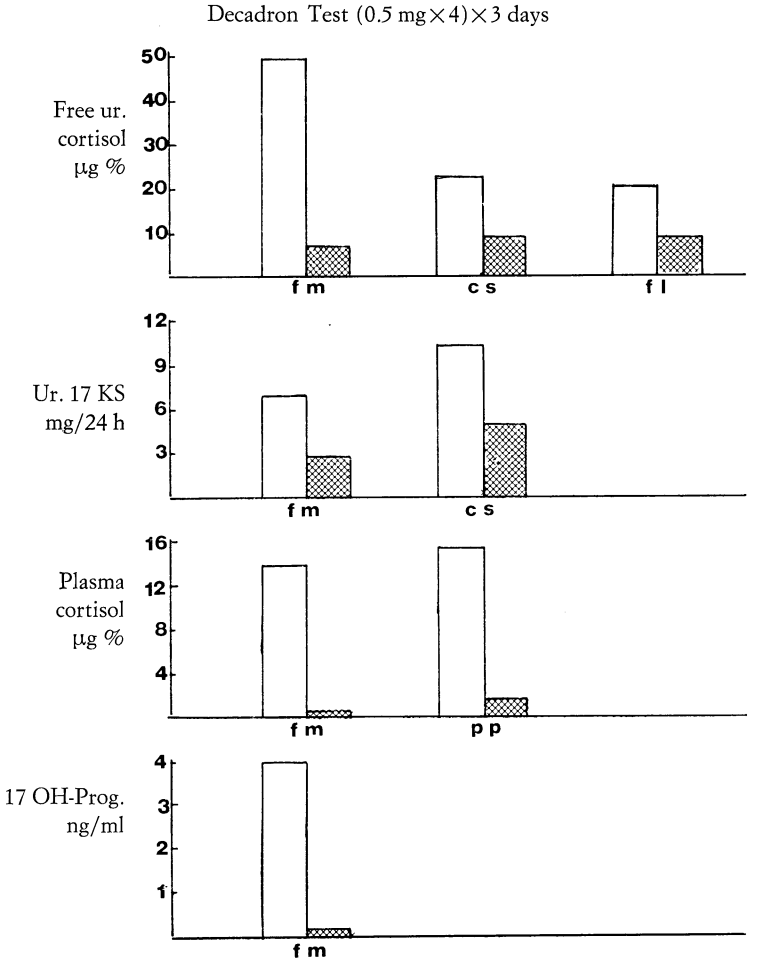

Fig. 1. — Free urinary cortisol, ur. 17-KS, plasma cortisol, plasma 17-OH progesterone before (white) and after desametazone administration (checked).

In all the examined patients the assay of 17-OH progesterone (tab. 2) confirmed its diagnostic usefulness: the values exceeded the normal range and therefore the interpretation of the pathology affecting these patients was definitely correct.

The same assay allows to diagnose deficits appearing in neonatal age very early, which is essential in the case of baby patients suffering from salt-loss-induced collapses ([12]).

Although this aspect is often neglected in literature, in all our patients we saw an increase in plasma testosterone which is theoretically justified given the level of enzymatic blockage of the adrenal steroidogenesis.

The other data, ACTH, plasma cortisol, free urinary cortisol, urinary 17 KS and DHEA-S, in the order, seem to be less significant.

Many Authors have stressed the importance of assaying ACTH which is almost always higher as a consequence of the cortisol production blockage. However, given the extreme variation of ACTH secretion, a single assay is unlikely to be diagnostically as important as some Authors claim ([13]).

ossification nuclei. Only under these conditions the therapy can achieve satisfactory results not only for the most apparent aspects of virilization (hirsutism, clitoridomegalia, muscular hypertrophy etc.) but also, and above all, for the stature growth which is definitely compromised if the connecting cartilages have already

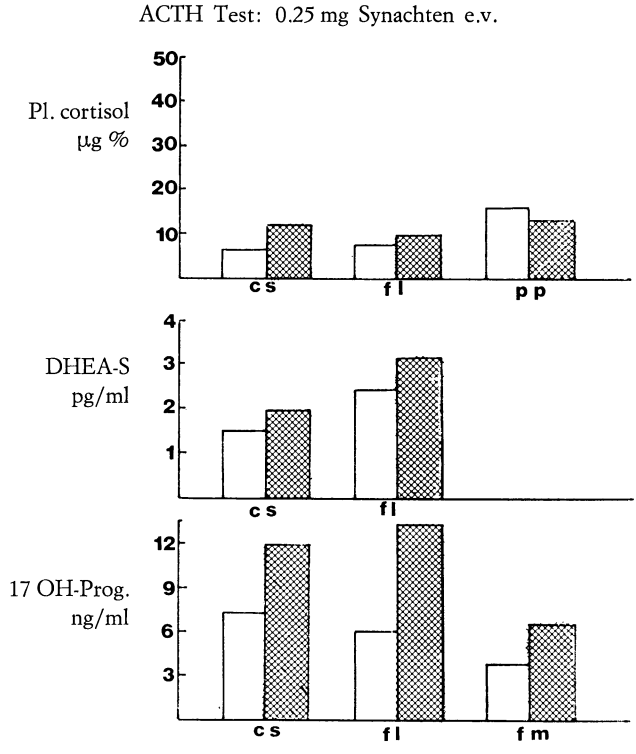

Fig. 2. — Cortisol, DHEA-S, 17OH-progesterone plasma levels before (white) and after ACTH administration (checked).

The reliability of the assessment of the bone age by left wrist and hand radiography and study of the appearance of the ossification nuclei at the various ages is absolutely unchanged. However, from a clinical point of view, we hope that the diagnosis can be established at an earlier bone age, that is when the androgenic effects have not yet materialized by stepping up the maturation of the joined up. According to our data, the Desametazone suppression test, which has recently been criticized by many Authors as being not enough specific in distinguishing between androgens of adrenal and ovarian origin, has confirmed its usefulness.

Free urinary cortisol, urinary 17 KS, plasma cortisol and 17 OH progesterone values, whose secretion is constantly con-

trolled by ACTH, decrease when corticotropin is suppressed. Such suppression is particularly clear in 17 OH progesterone and plasma cortisol which fall to extremely low levels.

The ACTH test confirms that adrenal gland is unable to produce cortisol in normal amount despite pharmacologic intervention.

Thus, the DHEA-S assay is, in our opinion, less useful than 17 OH progesterone response, which is particularly significant and important when its basal value is just above the normal threshold.

Therefore, our results confirm the essential diagnostic importance of the 17 OH progesterone assay. Its basal values, when high, already enable us to understand the syndrome; its values after ACTH stimulus can further confirm or show the enzymatic deficit when basal 17 OH progesterone is normal or just a little higher.

Let us finally recall that, according to the literature, the adrenal enzymatic deficit causes hirsutism more often than it is commonly believed and reaches a rather high incidence.

BIBLIOGRAPHY

1) Bongiovanni A. M.: *Human disorders of adrenal biogenesis.* In: James V. H. T., Serio M., Giusti G., Martini L. (eds.): *The endocrine function of the human adrenal Cortex.* New York, 1978; Academic Press, Inc., p. 265.
2) Bongiovanni A. M.: *Disorders of adrenocortical steroid biogenesis.* In: Sambury J. B., Wyngarden J. B., Fredrickson D. S. (eds.): *Metabolic Basis of Inherited Disease*, ed. 3, New York, 1972, McGraw-Hill Book Co., Inc., p. 857.
3) Prader A.: *Schweiz. Med. Wschr., 85*, 1955.
4) Klein R.: *Proc. Soc. Exp. Biol.* (N. Y.), 1958.
5) Crigler Jr. J., Silverman S. H.: *Pediatrics, 10*, 397, 1952.
6) Kowarsky A.: *J. Clin. Invest., 44*, 9, 1965.
7) Eberlein W. R.: *Pediatrics, 21*, 667, 1958.
8) Eberlein W. R., Bongiovanni A. M.: *J. Clin. Invest., 37*, 889, 1958.
9) Bisser H. K. A.: *Acta Pediatr. Scand., 56*, 216, 1967.
10) Childs B., Grumbach M. M., Van Wyk J. J.: *J. Clin. Invest., 35*, 213, 1956.
11) Gutai J. P., Kowarski A. A., Migeon C. J.: *J. Pediatr., 90*, 924, 1977.
12) Shackleton C. H.: *Pediatrics, 49*, 2, 1972.
13) Benato M., Boscaro M., Ridolfi P., Mantero F.: *Chronobiologia, 7*, 100, 1977.