STIMULATION TESTS IN ADRENO-GENITAL SYNDROME INDUCED BY 21 HYDROXYLASE DEFICIT

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SUMMARY

GnRH and TRH stimulation were performed on 4 patients affected by 21-β-hydroxylase adrenal deficit. Plasmatic FSH, LH, 17-β-estradiol, HPRL were assayed before and after GnRH, and HPRL before and after TRH.

The results seem to prove that these tests are useless for the diagnosis of adrenal enzymatic deficit.

On the other hand, they provide interesting additional information on physiopathological relations between adrenals and gonadotropins and between HPRL and adrenals.

INTRODUCTION

Adrenal 21-β hydroxylase deficit has been unquestionably proved to be congenital and therefore not acquirable during the course of life, as it was sometimes believed.

However, a deficit of this enzyme may become apparent late. This happens in cases of partial or limited deficit due to a changed (increased) hormonal demand by the organism, notably in puberty ([1, 2]).

Although most Authors believe the ovary to be the main source of hyperandrogenism in adult women, others say that adrenal enzymatic deficit is a frequent cause of hirsutism (46%) ([3]).

Since 21-β-hydroxylase is involved in the metabolic pathway of production of aldosterone and cortisol, its deficit causes accumulation of 17OH progesterone and, consequently, of androstenedione and testosterone. Hyperincretion of these androgens is responsible for the virilizing character of this syndrome.

Gynecologists are mainly concerned with mild and late forms appearing after puberty and presenting hirsutism, whether with menstrual irregularity or not, since more serious forms appear much earlier and are pediatricians' concern.

The simplest and more commonly followed method for detecting this enzymatic deficit is 17OH progesterone assay in basal conditions and after ACTH stimulation (which can identify least serious conditions when basal 17OH progesterone is normal or just higher).

Recently some Authors ([4]) have assayed basal values and values after gonadotropins and prolactin stimulation, respectivelv by GnRH and TRH, in patients with deficit. A hyperresponse has often been observed.

This study wants to check these preliminary data to improve the understanding of physiopathologic mechanisms that rule this syndrome and to evaluate the possibility of using these tests for clinical diagnosis.

Table 1. — *LH, FSH, HPRL, 17-β-estradiol values in basal conditions and after stimulation by GnRH (Relisorm, 100 mcg e.v.) in F.L.*

Time	LH mUI/ml	FSH mUI/ml	HPRL ng/ml	17βE₂ pg/ml
9 a.m.	3.5	5.2	11.0	48.7
15′	47.7	7.3	14.8	41.2
30′	74.4	9.5	11.5	55.6
45′	60.1	6.5	7.9	46.0
60′	42.5	8.3	7.7	65.4
11 a.m.	44.5	10.2	8.6	81.1
15′	260.0	19.4	12.0	90.4
30′	373.0	22.9	10.4	88.1
45′	277.0	33.3	10.5	147.4
60′	199.0	22.1	10.2	167.3
13 p.m.	130.0	25.5	19.3	32.7
15 p.m.	54.6	18.9	14.0	85.5
17 p.m.	18.8	11.2	8.9	218.8

MATERIAL AND METHODS

Our study concerns 4 female patients (age range: 13-19) with diagnosis of 21-β-hydroxylase deficit in post-puberal age. None of them reported menstrual irregularity. In the first half of the cycle they all underwent the following tests:

GnRH test

This test was performed by double stimulation with a 2-hour interval. For each stimulation 100 mcg Relisorm (Serono) were injected e.v. and blood sampling was performed in basal conditions and at 15′, 30′, 45′ and 60′ after injection. The test started at 9 a.m. Moreover, samples were taken 4, 6 and 8 hours after the first GnRH stimulation.

The plasma, obtained by immediate centrifugation and stored at −20 °C, was assayed for the following hormones: FSH, LH, HPRL (RIA method, Biodata kits) and 17-β-estradiol (Eirria kits).

TRH test

This test was performed at 9 a.m. with e.v. injection of 200 mcg TRH (Serono) and sampling in basal conditions and at 10′, 20′, 30′, 40′, 50′, 60′, 90′ and 120′ after stimulation.

The plasma obtained by immediate centrifugation was kept at −20 °C and assayed for prolactin (RIA method, Biodata kits).

RESULTS AND DISCUSSION

We performed GnRH test by double stimulation in order to reduce the risk of false negatives, since single stimulation sometimes fails in originating significant hypophyseal response despite the absence of organic or functional damage ([5-8]). Table 1, 2, 3, 4 list hormonal values in basal conditions and after GnRH test.

In F.L. and F.M. the first GnRH stimulation produced a pathological increase in gonadotropins – concerning LH only in F.L. – although basal values were normal.

The second stimulation fully confirmed the previous picture.

It is well-known that high LH and low FSH basal levels, combined with high LH and low FSH response to GnRH stimulation, suggest the presence of micropolycystic ovary ([9, 10]).

This behaviour is ascribable to permanent hyperestrogenism which is responsible for positive feed-back on LH and negative feed-back on FSH. In our cases the enzymatic deficit is likely to contribute to F.L.'s and F.M.'s relatively higher 17-β estradiol values which are probably responsible for gonadotropin hyperresponse to GnRH.

Table 2. — *LH, FSH, HPRL, 17-β-estradiol values in basal conditions and after stimulation by GnRH (Relisorm, 100 mcg e.v.) in F.M.*

Time	LH mUI/ml	FSH mUI/ml	HPRL ng/ml	17βE₂ pg/ml
9 a.m.	13.5	8.5	17.7	106.8
15′	>100	16.6	30.8	115.9
30′	>100	26.1	37.7	114.8
45′	>100	82.0	40.3	98.0
60′	>100	>100	49.7	115.9
11 a.m.	>100	>100	32.6	111.0
15′	>100	>100	32.9	95.2
30′	>100	>100	49.0	111.3
45′	>100	>100	44.8	107.1
60′	>100	>100	50.9	106.7
13 p.m.	>100	>100	51.4	94.1
15 p.m.	>100	>100	73.4	97.2
17 p.m.	>100	>100	25.9	88.2

Table 3. — *LH, FSH, 17-β-estradiol values in basal conditions and after stimulation by GnRH (Relisorm, 100 mcg e.v.) in C.S.*

Time	LH mUI/ml	FSH mUI/ml	HPRL ng/ml	17 β E_2 pg/ml
9 a.m.	9.4	6.9	9.8	18.5
15′	25.4	9.0	15.0	17.3
30′	36.2	9.5	38.1	15.9
45′	36.9	12.0	46.8	22.3
60′	37.1	8.8	26.4	53.3
11 a.m.	53.2	16.1	50.8	36.3
15′	63.8	21.3	47.3	36.5
30′	68.4	27.6	56.9	29.0
45′	79.2	31.1	53.7	25.5
60′	61.7	38.4	65.1	22.6
13 p.m.	54.0	30.8	39.6	50.9
15 p.m.	44.2	26.0	73.4	114.7
17 p.m.	13.1	16.9	13.0	117.4

Table 4. — *LH, FSH, HPRL, 17-β-estradiol values in basal conditions and after stimulation by GnRH (Relisorm, 100 mcg e.v.) in C.N.*

Time	LH mUI/ml	FSH mUI/ml	HPRL ng/ml	17 β E_2 pg/ml
9 a.m.	6.6	6.1	6.1	19.9
15′	25.4	6.6	5.5	17.4
30′	38.6	14.7	8.0	29.3
45′	34.6	9.3	4.7	18.3
60′	21.1	6.8	5.1	14.7
11 a.m.	26.9	11.7	6.2	29.4
15′	60.5	12.0	6.0	24.3
30′	78.1	17.2	6.2	33.9
45′	41.5	9.6	6.3	29.1
60′	38.3	13.0	6.3	40.8
13 p.m.	18.4	11.7	11.4	37.8
15 p.m.	20.4	12.2	12.8	74.4
17 p.m.	8.3	9.6	7.5	133.1

This situation is in accordance with the results reported by Carmina *et al.* (4).

On the other hand, interpretation of FSH hyperresponse to both GnRH stimulations in F.M. raises some doubts.

These initial data confirm the aspecificity of GnRH response in the polycystic ovary syndrome, since a similar picture can be seen in our cases and, probably, in all situations of hyperestrogenism, whether originating from the ovary or from the periphery. Basal prolactin had always kept within normal levels, but it did not during GnRH test (which is supposed to change these levels). As a matter of fact, we observed significant prolactin increase in C.S. and F.M. after the first and, particularly, after the second stimulation by Relisorm.

Similarly, the response to TRH (fig. 1) was again higher in C.S. and F.M. In our opinion, this coincidence of response to aspecific (GnRH) and specific (TRH) stimulation is important.

Several works dealing with relations between prolactin and adrenals have recently been published. Prolactin is commonly believed to stimulate adrenal steroidogenesis, as far as androgens only are concerned, notably on the way of Δ-5

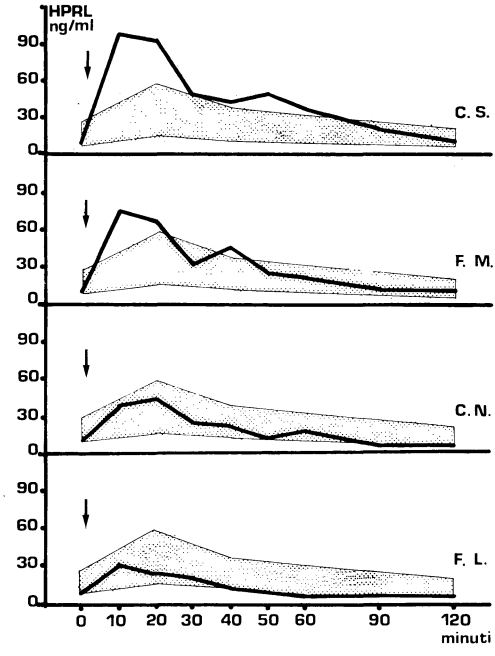

Fig. 1. — Plasma prolactin response to TRH test (↓ TRH 200 mcg e.v.) in 4 patients affected by 21-β-hydroxylase deficit.

with DHEA-S, DHEA and Androstenediol increase.

Moreover, the prolactin response to TRH stimulation was found to be significantly higher in patients affected by hirsutism than in control ones. Apparently hirsutism entails hypothalamo-hypophyseal disruption – the meaning of which is still unclear – and causes abnormal prolactin secretion after TRH stimulation.

Hirsutism is known to be the main characterizing feature of the 21-β hydroxylase deficit-induced adreno-genital syndrome; this aspect is related to enzymatic deficit-induced androgenic hyperincretion.

With regard to the earlier described prolactin/adrenals relations, it is important to stress that a prolactin synergic effect may also occur in these adrenals with a further increasing of androgenic production. It may well be that this synergism does not occur in basal conditions but rather in the known situation of increased TRH secretion that generally appears under stress conditions.

The tests examined, though contributing to a better understanding of still unclear delicate physiopathologic mechanisms, do not seem to be particularly useful in the diagnostic field, since responses may vary and combine with other pathologic conditions.

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