

TESTOSTERONE AND 17-HIDROXIPROGESTERONE IN A BATCH OF WOMEN WITH CONGENITAL ADRENAL HYPERPLASIA WITH DELAYED DEBUT

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Abstract: Testosterone (T) is the main androgen hormone and 17-hydroxyprogesterone (17-OHP) is the most important marker of congenital adrenal hyperplasia (CAH) through deficit of 21-hydroxylase. The purpose of the study was to establish the alteration of these two hormones in a group of women diagnosed with the non-classic form of CAH. The study took into consideration 41 cases diagnosed with CAH, non-classic form, through the measurement of 17-OHP and ACTH testing. Regarding testosterone, 36,6% of cases had abnormally increased values. Although 63,4% of the cases had basal 17-OHP over the normal limit, in 95% of the cases, the stimulation test was necessary in order to confirm the diagnosis.

Keywords: congenital adrenal hyperplasia, testosterone, 17-hydroxyprogesterone, ACTH testing

Rezumat: Testosteronul (T) este principalul hormon androgen, iar 17-hidroxiprogesteronul (17-OHP), principalul marker al hiperplaziei adrenale congenitale (HAC) prin deficit de 21-hidroxilază. Scopul studiului a fost determinarea modificărilor celor doi hormoni la un lot de femei diagnosticate cu forma neclasică (cu debut tardiv) a HAC. Studiul a fost realizat pe un număr de 41 de cazuri diagnosticate cu HAC cu debut tardiv, prin dozarea 17-OHP și a testului la ACTH. În cazul testosteronului, 36,6% din cazuri au avut valori anormal crescute. Deși 63,4% din cazuri au avut 17-hidroxiprogesteronul bazal peste normal, 95% au necesitat testul de stimulare pentru confirmarea diagnosticului.

Cuvinte cheie: hiperplazia adrenală congenitală, testosteron, 17-hidroxiprogesteron, testul la ACTH

INTRODUCTION

The daily production of testosterone in a normal adult woman is of 0,2-0,3mg per day. The ovary contributes with almost 20-30%, the suprarenal with 10% and the rest of 60% derives from the peripheral conversion of androstenedione and dehydroepiandrosterone (DHEA) (5).

In case of CAH, due to the enzymatic block, the production of suprarenal androgens is increased, altering the contribution of the two sources to the androgenic equilibrium (2).

PURPOSE OF THE RESEARCH

The purpose of the research was to establish the alterations of T and 17-OHP in a batch of women diagnosed with the non-classic form of CAH.

MATERIAL AND METHOD

The study was accomplished on a number of 41 cases, recruited out of a total of 1132 women with hyperandrogenic symptomatology, based on the following criteria:

Inclusion criterion:

- Basal 17-OHP more than 4ng/ml or positive ACTH stimulation test (17-OHP > 3,2ng/ml).

Exclusion criteria:

1. Other causes of hyperandrogenism: polycystic ovary syndrome, Cushing's syndrome, tumours (ovary, suprarenal, hypophysis), iatrogenic hyperandrogenism.
2. Negative ACTH testing (17-OHP < 3,2ng/ml).

T and basal 17-OHP were established in all 41 cases. In case, basal 17-OHP was below 4ng/ml, ACTH testing was made. The stimulation test was performed with tetracosactid, 0,50mg intramuscular, by measuring 17-OHP, 24 hours after administration.

Hormones establishment was made out of the venous blood. The sampling was made in the morning in follicular phase (day 4 and 9 of menstruation). In case the patients took oral contraceptives, or if they had anovulation, the blood sampling was made irrespective of the date of the last menstruation.

Testosterone dosing was made through the technique of the quantitative chemiluminescence immunodetermination with „Access Immunoassay Systems” and by using the devices and reagents of Beckman Coulter Inc. company. For 17-OHP, the quantitative ELISA was used, with IBL-Hamburg reagents. (1). The values which were considered normal were the following:

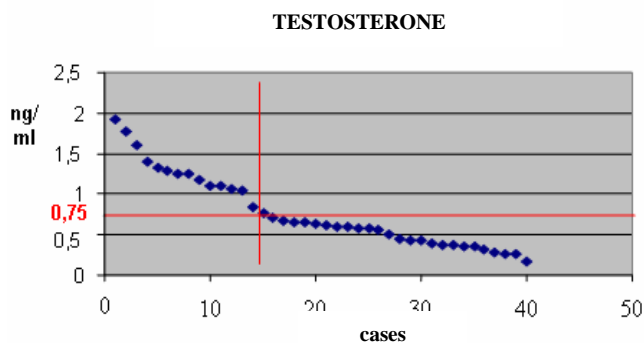
- Testosterone: < 0,1-0,75ng/ml
- 17OHP:- follicular phase: 0,3-1,0ng/ml
- luteal phase: 0,2-2,9ng/ml
- ACTH stimulation test < 3,2ng/ml

RESULTS AND DISCUSSIONS

Before the treatment, testosterone had values between 0.161 and 1,93ng/ml, with an average value of 0.75ng/ml.

In decreasing order, regarding the recorded values, 26 cases, that is 63,4%, are below the average values, while the rest of 15 cases, that is 36,6 %, are above this average. (Picture no. 1).

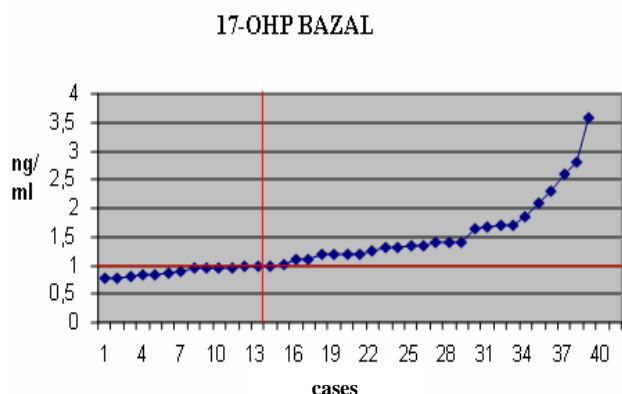
Picture no. 1.: Distribution of testosterone values in comparison with the average value.



Basal 17-OHP in the patients of our batch registered values between 0,78 and 20ng/ml, with an average of 2,239ng/ml. Statistically speaking, 37 of the cases were placed above the value of 2,7ng/ml; there were two cases with values between 2,7ng/ml and 4,6, respectively between 18 and 20ng/ml.

By eliminating the two cases with increased basal values, in which the stimulation test was not necessary, an average of 1,36ng/ml was obtained. Placed in increasing order as against this average, I found 13 cases, that is 33,3%, below this value , while the rest of 66,6 % cases exceeded this value (Picture no. 2)

Picture no. 2: Distribution of basal 17-OHP values as against the average values.

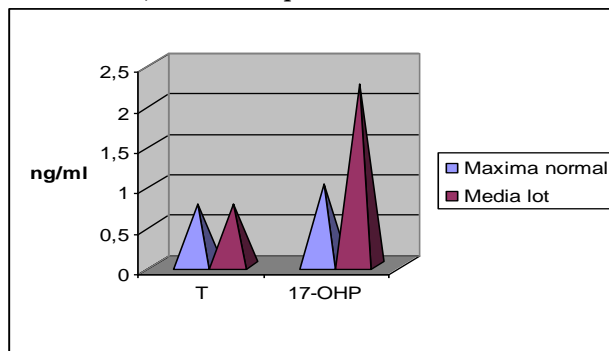


In comparison with the average of the testosterone values, the average of 17-OHP values, as against the maximum of the respective normal values is shown in picture no. 3

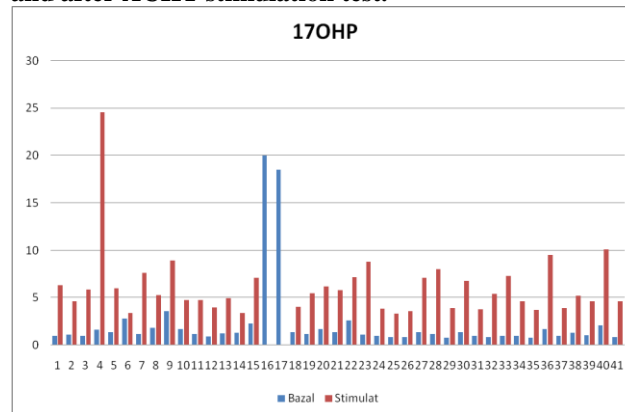
The values of **17-OHP stimulated** with ACTH were between 3,3 and 24,6ng/ml, with an average of 6,113ng/ml.

Comparatively, the values of 17-OHP before and after the stimulation (ng/ml) are emphasised in picture no. 4.

Picture no. 3: Comparison between the average of testosterone values and 17-hidroxiprogesterone in the studied batch, with the respective normal values.



Picture no. 4: Values of 17-hidroxiprogesterone before and after ACHT stimulation test.



The statistic difference between the basal and stimulated 17-OHP is of <0,0001, while the statistic correlation is 0,0730.

In the patients of our batch, **testosterone** has an average value of 0.752ng/ml; it is a value placed at the lower limit of the accepted values (picture no. 1). The average value for the population considered normal is of 0,29ng/ml for the plasmatic testosterone regarding the reagent used (1); obviously a smaller value than that of the batch studied by us.

26 cases, that is 63,4% are below the average value, while the rest of 15 cases, that is 36,6% exceed this average.

This observation indicates the fact that in case of CAH with delayed debut, the plasmatic testosterone is not necessarily high, the hyperandrogenic manifestations being the result of the weak suprarenal androgens (androstenedione or DHEA), converted at cellular level in testosterone and then in dihidrotestosteron under the action of 17β-hidroxiesteroidehidrogenaza, respectively 5α-reductaza (4). Other studies also consider that, in case of CAH, it is not necessary that testosterone should be

CLINICAL ASPECTS

high; usually, 17-OHP, progesterone and androstenedione are over the normal values (4).

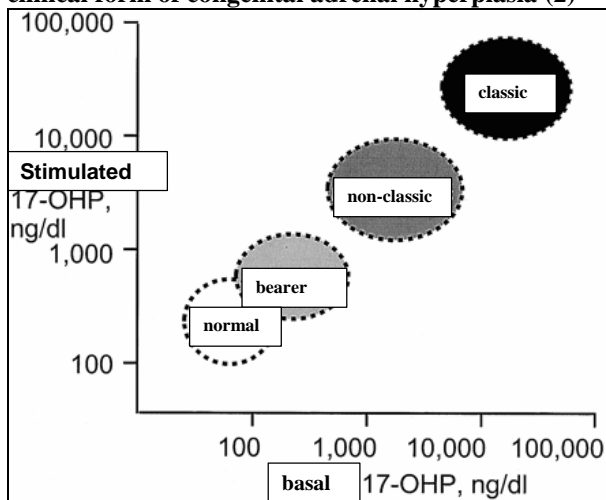
Basal 17-OHP in the patients of our batch has an average value of 2,23ng/ml, value that is over the normal value in the follicular phase when the sampling took place. For the reference population, the average for the reagent used is of 0,675ng/ml (1). This average value is below the inferior limit of the interval 2-4ng/ml, case in which the majority of authors (2,3,5) consider that CAH diagnosis has a high probability, but still uncertain, thinking that ACTH test stimulation is necessary. The same authors consider that the values above 4ng/ml have a sensitivity of 90% for the diagnosis of the non-classic form of CAH. There were only two cases (4,8%) in this situation in our batch, the majority of cases having values below 4 ng/ml, and for this reason the stimulation test is necessary.

By comparing this with the average of the basal testosterone, which is at the upper limit of normality, in case of 17-OHP, the average of the basal values exceeds more than twice the values accepted for the maximum of the follicular phase (1,0ng/ml) (picture no. 3).

If we take into consideration only the cases in which the ACTH stimulation test was made, we observe an average value of 1,36ng/ml, which is close to the maximum normal values, as in case of testosterone. By relating this average to the upper value of normality, an inverse distribution as against the testosterone could be observed, with only 33,3% cases below the average value and with 66,6% cases which exceed this values (picture no. 2)

We may conclude that in case in CAH with delayed debut, the basal values of 17-OHP over the upper limit of normality are more predictive for diagnosis, than the values of testosterone, abnormally increased.

Picture no. 5. ACTH stimulation test according to the clinical form of congenital adrenal hyperplasia (2)



Values of **17-OHP stimulated** with ACTH are between 3,3 and 24,6ng/ml. (picture no. 4), with an average of 6,11ng/ml. In literature (9,10,11), there are values of at least 10ng/ml, for the classic form with

virilization, while in the non-classic form of the disease, the values of stimulated 17-OHP are below 1,5 and 10ng/ml (picture no. 5).

As against the average of the basal values of the patients who were submitted to the stimulation test (1,36ng/ml), the average of the stimulated values is 4,5 times higher (picture no. 43), with a significant difference from the statistic point of view, between the two groups of values ($p < 0,0001$).

CONCLUSIONS

In non-classic form of CAH, testosterone is increased only in one third of cases. In 95% of the cases with non-classic form of CAH, the values of 17-OHP are not pathognomonic, requiring ACTH stimulation test.

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