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The ACTH test in the diagnosis of hirsutism

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The ACTH test has been used to confirm the diagnosis of adrenal insufficiency and the classic and the non-classic adrenal hyperplasia due to the 3-HSD, 21 OH e 11OH deficiencies. This article reviews the historical aspects of the use of ACTH in the diagnosis of hirsutism and points out its mains indications. In spite of new biological molecular advances in the diagnosis of adrenal enzymatic deficiencies, the use of the ACTH test can help the physician to predict both genothipus and fenothipus in populations with hyperandrogenic manifestations due to non-classical or late-onset congenital adrenal hyperplasia.

UNITERMS: ACTH, diagnosis, hirsutism, adrenal hyperplasia

INTRODUCTION

Historical aspects

Since the introduction of the test involving infusion of pituitary adrenocorticotropin hormone (ACTH) in 1948,¹ clinicians and gynecologists in general have been using the method to evaluate adrenal function in patients suspected of having adrenal insufficiency or congenital adrenal hyperplasia.

As far as the gynecological aspects are concerned, clinicians must be alert to the interpretation of the test; recent publications point out that patients with congenital adrenal hyperplasia in its late-onset or non-classical form may present a clinical picture consisting of irregular menses, hirsutism and other hyperandrogenic manifestations.

ACTH is a physiological agent that stimulates the biosynthesis of the adrenal cortex layers and is directly

stimulated by the corticotropin releasing factor (CRF) of hypothalamic origin. Thus, the adrenal cortex is evaluated clinically on the basis of its response to ACTH administration.

At first the test was used only for patients with adrenal insufficiency² and was considered to be costly and highly complex. With the advent of cosyntropin, a synthetic ACTH derivative that reduced allergic phenomena, the test started to be used to diagnose late-onset synthesis deficiencies, i.e., the non-classical cases suspected of congenital adrenal hyperplasia.

Most reports unanimously state that after ACTH stimulation, there is an important increase of almost all androgen precursors; for this reason, the test may identify patients with late-onset 21-OH (21-hydroxilasis) and 11-OH deficiency (11-hydroxilasis), as well as 3-HSD (3-hydroxysteroid dehydrogenasis) deficiency.³

Thus, the test started to be employed more frequently in the late 1960s, with different doses and routes being used.^{4,5} Today, the test is performed by intravenous infusion of 0.25 mg ACTH^{1,2} followed by blood collection 30 to 60 minutes later. The test can determine with precision the glandular adrenal reserve for each hormone separately. By studying the relationships between the hormones and their respective precursors, it is possible to determine diagnostic patterns for the deficiency of enzymes possibly

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involved in the etiology of hyperandrogenism, especially 3-hydroxysteroid dehydrogenase (3-HSD, 21-hydroxylase (21-OH) and 11-hydroxylase (11-OH)).⁶

Despite the established use of the test, the literature is not unanimous about its indication. CHETKOWSKI et al., after evaluating patients with late-onset 21-OH deficiency, concluded that the ACTH test does not precisely identify these patients, in addition to being excessively costly.⁷

DIAGNOSTIC OF THE ENZIMATIC DEFICIENCIES

In the detection of late-onset 21-OH deficiency, measuring 17-OH-progesterone after stimulus provides an important source of additional information.⁸ The diagnosis of this deficiency is based on the evaluation of plasma 17-OH-progesterone levels; however, the literature has reported different interpretations of the test.

AZZIZ & ZACUR consider women to be carriers when their 17-OH-progesterone levels exceed 1200 ng/dl after intravenous ACTH infusion.⁸ In contrast, DEWAILLY et al. suggested that patients with 17OH-progesterone levels exceeding 500 ng/dl which are reduced by dexamethasone should not be submitted to the ACTH stimulation test as they would be considered to have non-classical 21-OH deficiency. When these values are between 200 and 500 ng/dl, the patient would be considered borderline and should be submitted to the test. Those with levels of less than 200 ng/dl would not be considered to have late-onset 21-OH deficiency.⁹

In the Endocrine Gynecology Sector of the Department of Gynecology, Escola Paulista de Medicina, Federal University of São Paulo, we use the NEW nomogram to evaluate these patients. With respect to 11-OH deficiency, which is much more rare, measurement of compound S basely and after ACTH is also helpful for diagnosis. There are no clear criteria to identify these patients.

To evaluate 3-HSD activity, the diagnostic criteria most frequently employed were those proposed by PANG et al., i.e.: 1. post-stimulus 17-OH-pregnenolone levels two standard deviations above the levels detected in normal women (5 17OH-P>1639 ng/dl or 49.2 nmol/l); 2. post-stimulus DHEA levels two standard deviations above the levels observed in normal women (DHEA>1818 ng/dl or 63.1 nmol/l); 3. 17OH-pregnenolone/17OH-progesterone ratio two standard deviations above the values detected in

normal women (17OH-progesterone>6.4); and 4. 17OH-pregnenolone/cortisol ratio two standard deviations above normal values (17OH-pregnenolone/cortisol>52).¹⁰

Although these diagnostic criteria are widely accepted, they are not unanimously endorsed. GIBSON et al. used pregnenolone measurements,¹¹ whereas LOBO & GOEBELSMAN used a standardized DHEA-S measurement as a criterion.¹² Other authors have emphasized the DHEA/androstenedione ratio,⁵ whereas REDMOND et al. prefer the use of urinary metabolites.¹³

The tetracosatide depot (ACTH-depot) forms a complex with zinc hydroxide when used in the intramuscular form, with a slow and chronic ACTH release for a period of no less than 36 to 48 hours. Clinically, it is used in situations in which it is desirable to increase serum cortisol levels. Like intravenous ACTH, it can also be used to diagnose adrenal synthesis deficiencies due to the more potent and prolonged stimulus it provides for the three adrenal layers, chronically depleting their production.

PRATA LIMA, in a study of the effect of ACTH on normal women and women with idiopathic hirsutism, suggested criteria for the diagnosis of 3-HSD deficiency after detecting a considerable increase in the hormones of the fasciculated layer and a significant elevation of peripheral androgens such as S-DHEA and testosterone, a fact that is not observed when intravenous ACTH is used.¹⁴

CONCLUSIONS

Today, some reports tend to disregard the ACTH test. There are two reasons behind this attitude. The first has to do with the fact that 21-OH deficiency, by being linked to the HLA system, would not require the test but simply an analysis of these histocompatibility antigens. However, the cost of, and difficult access to this procedure are not taken into consideration. BARNES et al. stated that the excessive number of patients with 3-HSD deficiency reported over the last few years should be considered with some caution since there may be other changes in steroid metabolism that simulate this defect.¹⁵ However, the fact that an HLA-linked antigen for the deficiency has not yet been identified cannot rule out the test.

Thus, the test using ACTH stimulation by the conventional method or use of the ACTH-depot may be of help in the reproductive and endocrine function of women in general with menstrual and aesthetic repercussions.

RESUMO

O teste com ACTH tem sido utilizado para diagnosticar patologias como a insuficiência supra-renal, e as formas clássica e não-clássica de hiperplasia supra-renal em decorrência de deficiências enzimáticas. Revisou-se vários aspectos históricos envolvendo o uso do ACTH no diagnóstico do hirsutismo e são analisadas suas principais indicações. Apesar dos novos avanços em biologia molecular no diagnóstico das deficiências enzimáticas das supra-renais, o uso do teste com ACTH pode ajudar o clínico a prever o genótipo e fenótipo dos indivíduos que apresentam manifestações hiperandrogênicas devido à hiperplasia congênita da supra-renal na sua forma não-clássica.

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