35 - HYPERANDROGENISM AND VIRILIZING OVARIAN TUMOR

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INTRODUCTION

The hyperandrogenic syndromes include diseases that are manifested by an increase in biological activity of androgen (MARCONDES, 2006). The maximum clinical expression of hyperandrogenism is virilization (AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS, 2001).

Several etiologies may cause hyperandrogenism in women from a staff of hormonal imbalance in the ovaries and adrenal glands (polycystic ovary syndrome - PCOS and congenital adrenal hyperplasia - non-classic form) to the ovaries or adrenal cancer.

The main cause of hyperandrogenism in women is functional ovarian or PCOS, which represents two thirds of hyperandrogenic women, and half the cases of PCOS is accompanied by functional adrenal hyperandrogenism. What makes the androgen-secreting ovarian tumors pathological conditions relatively rare (incidence of 10% compared to other types of ovarian tumors) who present with classic symptoms of hirsutism of sudden onset and rapid progression, as well as other important aspects of virilization (SPRITZ , 2002). According to the assumption, the objective of this study is to conduct a case report about hyperandrogenism caused by a virilizing ovarian tumor.

METHODOLOGY

This is a case report conducted at University Hospital Alcides Carneiro, Federal University of Campina Grande. Information was obtained through direct interview with the patient as well as the observation of the chart.

With respect to determinations ethical force in our country, there was the verbal consent of the patient, and the signature of a term of informed consent, according to the ethical observances of Resolution No. 196/96 which regulates research involving human human.

CASE REPORT

Female patient, 65 years on regular treatment for hypertension, diabetes and heart failure is admitted for investigation of virilization due to complaints of hair growth on face, abdomen, back and upper limbs, hair loss and gain of 5kg. On examination: presence of hairs on the back, abdomen, upper limbs and face. Ferriman & Gallwey index equal to 13.

Hormonal evaluation revealed: TSH = 2.91 mIU/mL (N: 0.45 to 4.5 mIU/mL), ACTH = 6.9pg/mL (N: 0 to 46), Cortisol (8 hours after the dexamethasone suppression 23h) = 11.59 (N: 20-70), 17-alpha-hydroxyprogesterone = 1.54 ng/mL (N: <0.7 ng/mL), Total Testosterone: 568 ng/dL (N: 15-75 ng/dL).

The imaging investigation showed: transvaginal pelvic ultrasound, adnexal regions showing heterogeneous formations such as to clarify the possible origin of ovarian, endometrial thickening for post-menopausal; Training hyperechogenic oval inside the uterine cavity. Abdominal CT: Increased volume of both uterine attachments is showing hypodense areas in the interior especially on the right, which may correspond to increase in volume of the ovaries with follicles inside (functioning? Cystic lesions?). Hysteroscopy: uterine cavity with preserved architecture, with standard atrophic endometrium, Endometrial polyps little.

HIRSUTISM AND VIRILIZING OVARIAN TUMORS

The androgen-secreting ovarian tumors are relatively rare pathological conditions, concomitant with hirsurtismo classic symptoms of sudden onset and rapid progression, as well as other important aspects of virilization (SPRITZ, 2002). Among cancers of the ovary concomitant with hyperandrogenism can be highlighted:

Arrenoblastomas or Androblastomas (tumor Sertoli-Leydig cell)	Teratomas
Tumors of granulosa-theca cells	Gonadoblastoma
Hilar cell tumors	Tecoma luteinized
Dysgerminoma	Luteomas

It is noteworthy that ovarian tumors may secrete hormones other than androgens as hCG, serotonin, thyroxine or estrogens.

The account of this case is developed on the main complaint of the patient based onavailable hirsurtism and androgenetic alopecia reported lasting about one year. As mentioned above, virilization symptoms of sudden onset and rapid progression are found tightly linked to ovarian neoplastic changes. However, one cannot rule out other diseases that many well underway with the increase in body hairiness only for this finding. Therefore the evaluation of hirsurtismo and symptoms of hyperandrogenism has a function for guiding the opening of differential diagnosis of hyperandrogenic syndromes.

The hyperandrogenic syndromes include diseases that manifest themselves through increased production and/or biological activity of masculinizing hormones (MARCONDES, 2006). In adult women, with biological activity is the development of manifestations such as hirsutism, acne, hair loss with standard androgen, menstrual abnormalities, infertility/early abortion and signs of virilization such as amenorrhea, atrophy of breast parenchyma, changes in tone of voice, redistribution of muscle mass and clitoromegaly. Pathophysiologically, hirsurtism developed this course of action of androgens on the skin/hair follicle and is dependent on factors such as their own levels of circulating androgens (free fraction), the degree of skin sensitivity to this hormone and the ability to interconvert androgenic hormones/estrogen and other steroid interconversions by the body. Importantly, there is not always a correlation between the concentration of circulating androgens and clinical

manifestations, and these manifestations associated with more, so the rate of production of testosterone, ie, the amount of testosterone produced by the body in 24 hours. Thus the signs of virilization are present when there is marked increase in the rate of production of testosterone which, in general, but not necessarily, be accompanied by corresponding increase in serum concentrations of the hormone. This pattern is characteristic of functioning tumors of the ovary and adrenal and ovarian hyperthecosis, but may also occur in the classic form of congenital adrenal hyperplasia.

As seen, a number of pathologies coursing with virilization and hyperandrogenism. However, it is necessary for differential diagnosis among those who attend only those capable of generating hyperandrogenism virilization. Therefore, the syndrome can be classified didactically hyperandrogenism, facilitating the diagnostic search in virilization virilizing or not (See figure 1).

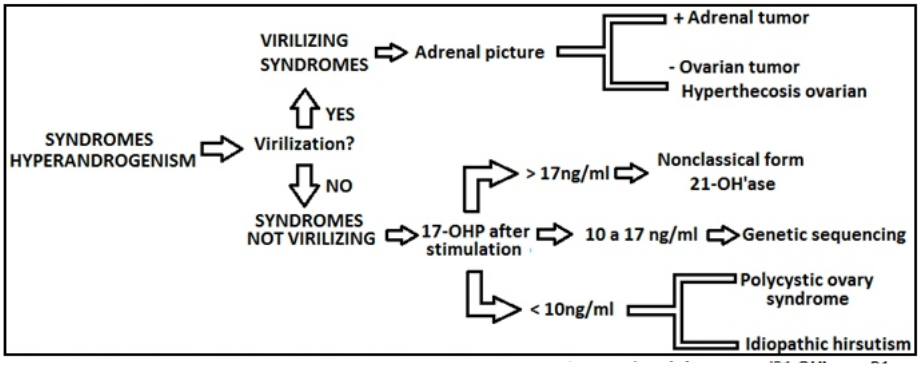

Figure 1. Flowchart for the investigation of hyperandrogenic syndromes in adult women (21-OH'ase: 21-hydroxylase, 17-OHP, 17-hydroxyprogesterone).

(Source: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302006000600019)

The virilizing syndromes are characterized, the pathophysiologic point of view, the increase in circulating androgens and clinically for signs of virilization. The pathologies that course with this condition are usually neoplastic diseases (ovarian and adrenal tumors) and functional (hyperthecosis ovarian stromal hyperplasia or cortical). Laboratory, 80% of patients have serum total testosterone, greater than 200 ng/dL (MAROULIA, 1981). It is worth mentioning that the diagnosis of a virilizing syndrome is mainly clinical, ie, in the absence of signs of virilization discard the hypothesis.

It does not virilizing hyperandrogenic syndromes are characterized by present production rate of testosterone is low, no signs of virilization, and a concentration of testosterone normal or slightly elevated, infrequently greater than 200 ng/dL. This syndrome is represented by a non-classical 21-hydroxylase deficiency, idiopathic hirsutism and the Polycystic Ovary Syndrome.

As reported, the clinical evaluation is essential for the development of diagnostic hypotheses and to guide further investigation since the signs and symptoms are virilizing defining the poles of an investigation of Androgenic syndromes. The history should clarify the patient's age, time of onset of hirsutism in relation to puberty / menopause, the installation mode (progressive or abrupt and fast), its evolution (as measured by the number of monthly waxing), intensity of acne and seborrhea the menarche, the duration and frequency of menstrual cycles, the notion of possible ovulation, ethnicity, family history, previous medical treatments that may have included the use of steroids, which the contraceptive method used in this and the patient has an active sex life. Should also be investigated the presence of symptoms suggestive of thyroid or adrenal dysfunction and hypoestrogenism. Regarding the physical examination should include in particular the anthropometric measurements such as BMI and waist / hip ratio (evaluating patients with higher metabolic risk); topography/body hair pigmentation and the usual signs that may accompany hirsutism, acne and seborrhea and possibly, alopecia. It is suggested the use of a semi-quantitative classification of the degree of hirsutism - the Ferriman and Gallwey score - for the initial evaluation and clinical (FERRIMAN & GALLWEY, 1961).

In terms of additional assessment is made to order tests, guided by the initial clinical evaluation. In patients with regular cycles confirmed that the query only isolated hirsutism, you can start treatment without the need for more elaborate laboratory evaluation. As for the hirsute patients with menstrual cycles or menopause are certain levels of androgens, prolactin, luteinizing hormone (LH), and the short ACTH test. If there is clinical suspicion for thyroidopathies, Chushing and androgen-secreting tumors (clinical history of rapid evolution and/or very high androgens) to analyze thyroid function, perform steroid suppression test and display imaging evaluation (abdominal ultrasonography, transvaginal ultrasonography and computed tomography abdominal), respectively. Moreover, in obese patients with a waist/hip ratio > 0.85, family history of diabetes or dyslipidemia is asked a lipid profile, fasting and post-2hs at least one glucose and fasting insulin dosage (recommending a diet for 3 days prior to at least 300 g carbohydrate/day).

The following therapeutic hirsurtismo aims to treat the basic etiology of hyperandrogenism, so measures to normalize androgen production in cases where there is an increase of, inhibit the action of circulating androgens and identify patients at higher risk for metabolic disorders and/or cancers of the reproductive tract are based.

In situations in which they identify associated endocrine disorders (thyroid disorders, hyperprolactinemia, Cushing's syndrome) a specific treatment should be performed. For the rarer cases of androgen-producing tumors - how to frame the case reported by this work - the most recommended treatment is surgery always taking into account the patient's age and stage and histopathological classification of the tumor. The following chemically/adjuvant radiotherapy is still controversial, but it is recommended for tumors with staging/prognostic larger and more reserved, respectively.

DISCUSSION

Hirsutism is defined as excessive growth of terminal hair in women, in areas characteristic anatomical distribution of male and is a major manifestation of hyperandrogenic syndromes (Spritz, 2002). It can manifest itself as a complaint alone or accompanied by other signs of hyperandrogenism (acne, seborrhea, androgenic alopecia), virilization (hypertrophy of the clitoris, increased muscle mass, changing the tone of voice), menstrual disorders and / or infertility or changes metabolic-related hyperinsulinemia/insulin resistance.

The present case report, it is a patient of 65 years known carrier of hypertension and diabetes mellitus type 2 and whose main complaint was generalized hirsutism, androgenic alopecia and weight gain. She was admitted to the endocrinology service University Hospital Alcides Carneiro - HUAC, first, for investigation of virilization on 21/07/2008, reporting the emergence

of such a picture for about a year.

The presence of signs of virilization and testosterone levels greater than 200mg/dL already leads to the exclusion of non-virilizing hyperandrogenic syndromes: the nonclassical form of 21-hydroxylase deficiency, idiopathic hirsutism and polycystic ovary syndrome.

The main hyperandrogenic syndromes who present with signs of virilization, such as the present report, are usually neoplastic diseases (ovarian and adrenal tumors) and functional (hyperthecosis ovarian stromal hyperplasia or cortical). A small overproduction of androgens can also be observed in patients with Cushing's disease in postmenopausal patients, in cases of pregnancy and patients undergoing treatment with androgens. Thus, the diagnostic hypothesis were adrenal hyperplasia, ovarian tumor and Cushing's syndrome.

The hyperthecosis is defined as a non-neoplastic ovarian disease, characterized by the presence of islet cells in ovarian stroma and thecal with clinical reminiscent of polycystic ovary syndrome (hirsutism and/or acne or androgenetic alopecia, chronic anovulation associated with the menstrual disorder type oligo/amenorrhea and infertility). However, the installation frame abrupt patient and testosterone levels of 568 ng / dl speak more in favor of tumor of the ovary or adrenal.

Virilizing adrenal tumors are rare and the clinical picture has abrupt onset and rapid progression. Following this hypothesis, the research protocol of hyperandrogenic syndromes, USP's Faculty of Medicine (USP) - see figure 2 below, the next step is to perform a CT adrenal gland, which defines such a resulting positive diagnosis. Probably to a better cost / benefit, was asked a total abdominal CT revealed an asymmetry in size between the adrenal glands lying to the left with larger dimensions in relation to the right.

Cushing's syndrome should be considered especially in patients presenting with central obesity, purple striae, hypertension and diabetes. The normal dosage of cortisol and ACTH in the patient to take away such a hypothesis. However, only the basal doses of these hormones are not sufficient to confirm the clinical diagnosis of Cushing's syndrome, requiring dynamic tests that stimulate or inhibit the hypothalamic-pituitary-adrenal axis. And so was asked to serum cortisol (8 am) after dexamethasone suppression to 23h which resulted in 11.59, helping keep such a hypothesis.

Other conditions such as thyroid disease, hyperprolactinemia, use of drugs (phenothiazines, danazol, metyrapone, cyclosporine, among others), can alter the secretion, transport and / or metabolism of androgens and lead to a framework of hirsutism. The patient's TSH is normal, other thyroid diseases. During the interview, the patient did not mention the use of any of the above mentioned agents which removes this drug etiology. It was requested the dosage of prolactin, which did not mean negligence, because there was no complaint of galactorrhea and suspected virilizing tumor was greater.

The androgen-secreting ovarian tumors are relatively rare, but should always be remembered as a cause of hirsutism, with recent onset and rapid progression with virilization important. And so, to confirm this etiology was requested imaging tests, in accordance with the flowchart of the service of Endocrinology and Metabolism FMUSP.

The transvaginal pelvic examination revealed enlargement of the right ovary. Cytopathology of the uterine cervix showed no abnormalities. Transvaginal Ultrasonography showed changes in endometrial thickness and adnexal regions not compatible with the situation in post-menopausal. Total abdominal CT confirmed the ovarian changes. Hysteroscopy revealed endometrial polyp.

Thus, with the exclusion of other causes and because of the changes observed in imaging studies confirmed the hypothesis of virilizing ovarian tumor.

Due to other diagnoses that the patient had been prescribed anti-hypertensive and NPH insulin dose adjustments are shown several of these medications because of the difficult to control hypertension and DM2.

For the definitive treatment of the tumor, surgery is most appropriate, taking into account patient age, histopathological staging and grading of the tumor. Thus, we performed bilateral anexectomia is not reported in the medical records of the holding or staging and the histopathological classification probably due to the large demand for the services of the H.U.A.C.

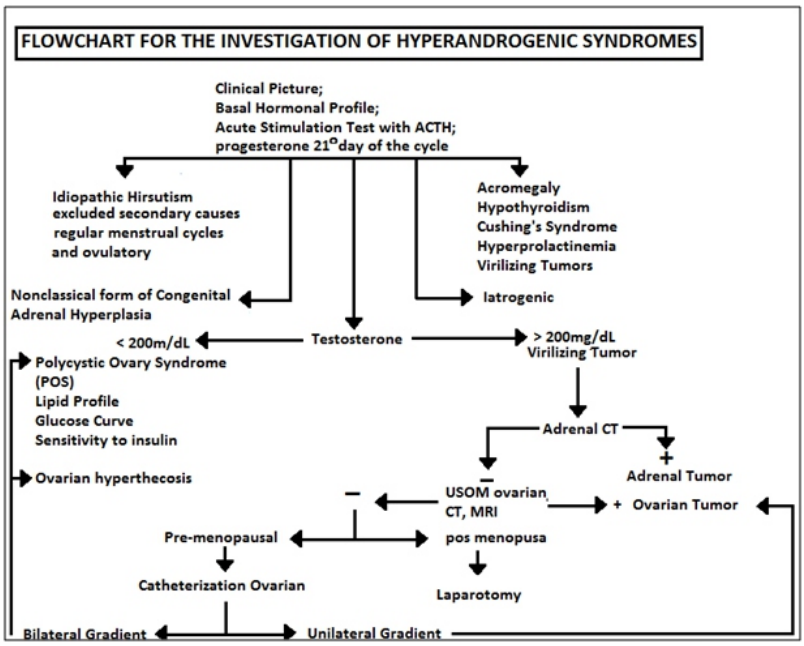

Figure 2. Flowchart of Research Hiperandrogenics Syndromes. FMUSP. + Positive, - negative.
(Source: http://www.fm.usp.br/endoresidentes/protocolo/prot_shiperandrogenicas.php)

FINAL THOUGHTS

Although not the most common etiology when faced with signs of hyperandrogenism and virilization virilizing ovarian tumors should be considered as differential diagnosis in postmenopausal women.

The hyperandrogenic syndromes include diseases that are manifested by an increase in biological activity of androgens. In adult women, these manifestations include hirsutism, acne, androgenetic alopecia type, menstrual dysfunction, infertility, miscarriage and early signs of virilization.

Importantly, there is not always a correlation between the concentration of circulating androgens and clinical manifestations. Thus, patients with hirsutism may have normal concentrations of androgens and vice versa. As such, it becomes necessary to carry out a detailed and careful investigation of cases of hyperandrogenism with broader approach including hormonal evaluation and imaging.

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HYPERANDROGENISM AND VIRILIZING OVARIAN TUMOR

ABSTRACT

The androgen-secreting ovarian tumors are relatively rare pathological conditions that happen with classic symptoms of hirsutism of sudden onset and rapid progression, as well as other important aspects of virilization. When it comes to rapid emergence of hyperandrogenic syndromes, always thinks of androgen-secreting ovarian tumors, although these conditions represent only 10% incidence in relation to other types of ovarian tumors. However, one cannot rule out other diseases that express your condition through increased production and/or biological activity of masculinizing hormones. Thus, signs of virilization are present when there is marked increase in the rate of production of testosterone which, in general, but not necessarily, be accompanied by corresponding increase in serum concentrations of the hormone. This pattern is characteristic of functioning tumors of the ovary and adrenal and ovarian hyperthecosis, but may also occur in the classic form of congenital adrenal hyperplasia. Through a case report were discussed the main features concerning the hyperandrogenic syndromes and hirsutism, highlighting key aspects of the diagnostic investigation, as well as the main differential diagnosis with special emphasis on the virilizing ovarian tumor.

KEYWORDS: Hyperandrogenism. Hirsutism. Ovarian Neoplasms.

HYPERANDROGÉNIE ET LA TUMEUR DE L'OVAIRE VIRILIZING

SOMMAIRE

Les tumeurs ovariennes sécrétant des androgènes sont relativement rares états pathologiques qui se produisent avec des symptômes classiques de l'hirsutismed'apparition soudaine et rapide progression, ainsi que d'autres aspects importants de virilisation. Quand il s'agit de l'émergence rapide des syndromes d'hyperandrogénie,pense toujours des tumeurs ovariennes sécrétant des androgènes, bien que ces conditions ne représentent que 10% d'incidence par rapport à d'autres types de tumeurs de l'ovaire. Cependant, on ne peut pas exclure d'autres maladies qui expriment votre condition grâce à une production accrue et/ou l'activité biologique des hormones de masculinisation. Ainsi, des signes de virilisation sont présents quand il ya augmentation marquée du taux de production de la testostérone qui, en général, mais pas nécessairement, être accompagnée d'une augmentation correspondante des concentrations sériques de l'hormone. Ce schéma est caractéristique de fonctionnementdes tumeurs de l'ovaire et hyperthecosis surrénales et des ovaires, mais peut également se produire dans la forme classique d'hyperplasie congénitale des surrénales. Grâce à unrapport de cas ont été discutées les principales caractéristiques concernant les syndromes d'hyperandrogénie et de l'hirsutisme, en soulignant les principaux aspects de l'investigation diagnostique, ainsi que le principal diagnostic différentiel avec un accent particulier sur la tumeur de l'ovaire virilisation.

MOTS-CLÉS: Hyperandrogénie. Hirsutisme. Néoplasmes ovariens.

HIPERANDROGENISMO Y UN TUMOR VIRILIZANTE DEL OVARIO

RESUMEN

Los tumores ováricos secretores de andrógenos son relativamente raras condiciones patológicas que se presentan con síntomas clásicos de hirsutismo de inicio súbito yrápida progresión, así como otros aspectos importantes de virilización. Cuando se trata de rápida aparición de síndromes de hiperandrogenismo, siempre piensa en los tumores ováricos secretores de andrógenos, aunque estas condiciones sólo representan el 10% de incidencia en relación con otros tipos de tumores de ovario. Sin embargo, no se puede descartar otras enfermedades que expresan su condición a través de una mayor producción y / o actividad biológica de las hormonas masculinizantes. Por lo tanto, signos de virilización se presentan cuando hay un marcado

aumento en la tasa de producción de testosterona que, en general, pero no necesariamente, ir acompañado por el correspondiente aumento en las concentraciones séricas de la hormona. Este patrón es característico del funcionamiento de los tumores del ovario y hipertecosis suprarrenales ylos ovarios, pero también puede ocurrir en la forma clásica de hiperplasia suprarrenal congénita. A través de un reporte de un caso se analizaron las principales característicasrelativas a los síndromes de hiperandrogenismo e hirsutismo, destacando los aspectosclave de la investigación diagnóstica, así como el diagnóstico diferencial con especial énfasis en el tumor ovárico virilizante.

PALABRAS CLAVE: Hiperandrogenismo. Hirsutismo. Los tumores de ovario.

HIPERANDROGENISMO E TUMOR VIRILIZANTE DE OVÁRIO

RESUMO

Os tumores ovarianos secretores de androgênios são condições patológicas relativamente raras que cursam com sintomatologia clássica de hirsutismo de início súbito e progressão rápida, além de outros aspectos de virilização importantes. Quando se fala em síndromes hiperandrogênicas de surgimento rápido, sempre se pensa nos tumores ovarianos secretores de androgênios, apesar destas condições representarem apenas 10% da incidência em relação a outros tipos de tumores ovarianos. Contudo, não se pode descartar outras patologias que expressam seu quadro clínico através de um aumento da produção e/ou da atividade biológica dos hormônios masculinizantes. Dessa forma, os sinais de virilização estão presentes quando há aumento acentuado na taxa de produção de testosterona que, em geral, mas não obrigatoriamente, é acompanhada de elevação correspondente nas concentrações séricas do hormônio. Tal quadro é característico das neoplasias funcionantes do ovário e adrenal e da hipertecose de ovário, podendo ocorrer também na forma clássica de hiperplasia adrenal congênita. Através de um relato de caso foram abordadas as principais características concernentes às síndromes hiperandrogênicas e ao hirsutismo, evidenciando aspectos fundamentais da investigação diagnóstica, bem como os principais diagnósticos diferenciais com especial destaque para o tumor virilizante de ovário.

PALAVRAS CHAVE: Hiperandrogenismo. Hirsutismo. Neoplasias Ovarianas.