ETHIOPATOGENIC DIAGNOSIS OF THE HYPERANDROGENIC SYNDROMS

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Abstract: *Hyperandrogenic symptoms are frequently encountered. Although the number of neoplasms is below 2% of the total of hyperandrogenism forms, there is need for an accurate assessment in order to exclude them. Most frequently encountered is the polycystic ovary syndrome (POS) (70-85%), followed, at distance, by the late onset congenital adrenal hyperplasia (1,5-4%). The diagnosis is based on medical history, physical examination and hormonal evaluation. The diagnosis of iatrogenic hyperandrogenism is made by interview and of the idiopathic one (5-15%) by exclusion.*

Keywords: *hyperandrogenism, tumour, polycystic ovary syndrome, congenital adrenal hyperplasia, idiopathic.*

Rezumat: *Simptomatologia hiperandrogenică este frecvent întâlnită. Deşi neoplaziile reprezintă sub 2% din totalul hiperandrogenismelor, o evaluare precisă trebuie să le excludă. Cel mai frecvent se întâlneşte sindromul ovarelor polichistice (70-85%), urmat, la distanţă, de hiperplazia adrenală congenitală cu debut tardiv (1,5-4%). Diagnosticul se bazează pe anamneză, examen fizic şi dozări hormonale. Diagnosticul hiperandrogenismului iatrogen este anamnestic, iar al celui idiopatic (5-15%) de excludere.*

Cuvinte cheie: *hiperandrogenism, tumoral, sindromul ovarelor polichistice, hiperplazia adrenală congenitală, idiopatic*

Hyperandrogenism is a term usually used in order to describe the most frequent clinical signs of the pilosebaceous system in the women with hyperandrogenemia or increased susceptibility to the androgen hormones actions: hirsutism, acne and alopecia. Hyperandrogenism may also bring about different organic, pathologic and functional alterations: female genital system, cardiovascular system, muscle-osseous system, adipose tissue and nervous system. (1) Taking into account the rather large frequency of certain signs (such as hirsutism) and the fact that the majority (95%) are determined by benign conditions, such as the Polycystic Ovary Syndrome or the idiopathic hirsutism, some authors consider that, regarding the easy and mild forms and with regular menses, the accurate establishment of the etiology is not of large importance. (7) Only in these cases, the investigations must be oriented towards the Polycystic Ovary Syndrome, by measuring testosterone, LH and FSH, (4,7) because on one hand, the investigations are quite expensive and on the other hand, the accurate establishment of the etiology in these cases is not so important for the treatment. Taking into consideration the possible metabolic effects of hyperandrogenism on long term (1,3) and the fact that an etiologic treatment could be less expensive even from the beginning, the etiologic diagnosis could be important, even from the beginning, within the limits of possibilities. First of all, the iatrogenic hyperandrogenism should be excluded through anamnesis (anabolishing, androgenic steroids, sodium valproate). (13) It is obvious that the main effort should be addressed to the most serious causes on short term. These are represented by the **tumoral pathology.**

The indices for the hyperandrogenic tumour pathology are:

1. basal testosterone above 200ng/dl (normal up to the value of 80ng/dl or 2,8nmol/l);
2. DHEAS above 700μg/dl (normal up to the value of 350μg/ml or 9,5μmol/l). (13,15)

In these conditions, the suppression test with DXM 5x2 mg must be applied. If it is negative, the *ovary* will be explored imagistically or even invasively and secondly, *the suprarenal*, in order to detect a malign or benign tumour secreted by androgens. If the DXM 5x2mg test comes positive, we talk about a functional hyperandrogenism and we should make research for *POS* in the first case and for *hyperprolactinemia* in the second case. (15) If the tumoral pathology is excluded, the etiologic diagnosis of hyperandrogenism is addressed to the most frequent causes, based on the anamnesis data, clinical examination and paraclinical data.

The polycystic ovary syndrome is considered the most frequent endocrinopathy of women, with a prevalence between 5-10% of the general population. (6) The present day criteria (Rotterdam 2003) impose two conditions out of three, in order to establish the diagnosis:

- Irregular menses due to oligo- or anovulation;
- Clinical hyperandrogenism manifestations (hirsutism, acne, androgenic alopecia) or paraclinical (hiperandrogenemia);
- Polycystic ovaries. (9,14).

Besides these inclusion criteria, there is also an exclusion criterion: it is important that hyperandrogenism should not be determined by other known reasons, such as: congenital adrenal hyperplasia, androgen secreting tumour, hyperprolactinemia, Cushing syndrome and acromegaly. (6,16) In exchange, the definition does not require the presence of the cystic ovaries for the diagnosis. These may be found in the normal population in a percentage of 16-23%. Regarding different populational studies, the aspect of polycystic ovary registered the following percentages: 92-94% women with idiopathic hirsutism; 30-40% hirsute and women with amenorrhea; 87% with oligomenorrhea; 82% with congenital suprarenal hyperplasia; 82% with type 2 diabetes mellitus; 40% with gestational diabetes mellitus family history; 83% with acne. (16)

Laboratory tests include increased levels of total, free and androstenedione testosterone, reduced SHBG, the relation LH/FSH>2, increased estrogens and prolactin.

Congenital adrenal hyperplasia (CAH) represents the second cause of hyperandrogenism. Here, 21-hydroxilase deficit is the most frequent cause (90-95%). (11) From the point of view of the clinical manifestations, there are two forms: classic and non-classic.

The classic form has an incidence of 1/5000-15000 births; it is more frequent in certain populations, such as the Yupik Eskimos from Alaska (1/300-700 births). The manifestations exist even from birth with phenomena of variable intersexualization. (12) After birth, the virilization of the little girls continues, as well as the acceleration of the somatic growth, with the premature closing of the development cartilages and low final height. Early menarche and heterosexual precocious pseudopuberty may also occur. (8) Without any treatment, the virilization phenomenon is progressive, accompanied by defeminization, sterility and all major manifestations of hyperandrogenism. (11) In certain cases, these manifestations of hyperandrogenism with virilization are accompanied by collapse due to hypoaldosteronism and hypercortisolism.

The non-classic form of the 21-hydroxilase deficit has a less known prevalence, being usually treated and diagnosticated as POS. (3) In New Zeeland, alterations of the 21-hydroxilase gene were found in 5% of the new born and regarding the symptomatic patients, in 7% of the children with sexual precocity and in 6% of the women with hirsutism. (11) Hyperandrogenism manifestations are similar with those for POS: they occur before puberty, bring about pilosebaceous manifestations and ovulatory dysfunctions and metabolic disorders on long term. Sexual precocity is characteristic. (5,8) Laboratory manifestations are also similar with those of POS. POS definition also includes the exclusion of other causes for hyperandrogenism; that is why, the diagnosis algorithm of this syndrome should include the 17-OHP dosage for the exclusion of CAH. (5) Levels of 17-OHP below 2ng/ml (6nmol/l) and above 4ng/ml (12nmol/l) have good negative, respectively positive predictive value. Between 2-4ng/ml (6-12nmol/l), ACTH stimulation test is recommended.

Idiopathic hyperandrogenism is considered the third cause of the hyperandrogenic syndrome. The term refers to the androgenic manifestation, usually from pilosebaceous level (acne, hirsutism) that are not due to other reasons (ovarian, suprarenal, tumour, thyroid, hyperprolactinemic), when the plasmatic androgens are normal and there is no ovulatory dysfunction. So, it is more a diagnosis of exclusion. The prevalence would be of 5-15% of the hirsute women, according to nationality and race. (2) An increased prevalence with familial character occurs in the Mediterranean woman or in those of the Eastern India. (3,16) The reason would be either the increase of the sensitivity of the androgenic receptor, or the alteration of the activity of certain enzymes that intervene in the tissular metabolism of the androgen hormones, such as 5-alpha-reductase, that transforms the testosterone in dihydrotestosterone (DHT). Due to the fact that this transformation takes place at intracellular level, there is no correlation between the level of DHT and hirsutism. (3) As a marker of DHT, its metabolite is used, that is the 3α-androstanediol glucuronide. (15) It is not a routine test or screening, this indicator being useful only when the plasmatic androgens are normal. (2)

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