REVIEW ARTICLE

Endocrinologic evaluation of acne

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ABSTRACT

Acne is one of the most frequent pathologies, and, most commonly, the only manifestation of an underlying condition. Its multifactorial etiology and demonstrated association with endocrine disorders, particularly hyperandrogenism, puts endocrinologic evaluation in the high-priority category. Not doing so may result on therapeutic failures and the missed diagnosis of systemic diseases.

INTRODUCTION

NAcne is a well-known highly prevalent chronic inflammatory disease. Up to 80% of people have suffered from this condition at some point in their lives, especially during puberty. It often persists into adulthood. Acne's most serious or persistent forms lead to psychosocial impact, which can affect the quality of life of patients.[1] Currently, due to the COVID-19 pandemic, there has been an increase in acne within the adult population, which may be associated with the use of masks;[2] the term "maskne" has originated, expressing a variant of acne mechanica secondary to follicular occlusion, dysbiosis, friction and pressure, all associated with mask use.[3] Although that could explain the etiology of some cases, it is evident that acne is considered as a condition with multifactorial origin, with one of its most important components being hormonal imbalance. Hence the importance of ruling out endocrine pathologies for proper treatment.

As early as 1949, Sulzberger and Baer, in the midst of an update of acne vulgaris, insisted on the hormonal influence on acne: "if one were forced to choose a factor without which acne vulgaris could not develop, one would surely select the endocrine factor". More than a century before, Bateman had already suggested that acne occurred "during the first part of life, from puberty to age thirty or thirty-five". Riolan is cited as the first one to observe an association between acne and menstrual alterations in 1638.[4] The 4 classic factors associated with the physiopathology of acne have been modified over time as a result of continuous research, becoming somewhat more complex, mainly described as an alteration of the sebaceous glands associated with hyperseborrhea and an alteration in the composition of sebum free fatty acids; imbalance of the hormonal microenvironment, interaction with neuropeptides, aberrant differentiation of the follicular epithelium and hyperkeratinization, inflammation and innate and adaptive Immunity alterations.[5]

DEVELOPMENT

The skin can be considered as an endocrine organ, since it has been shown that it can synthesize hormones which exert their biological effects by interaction of high affinity receptors in the pilosebaceous unit. Sexual hormones can be divided into 3 groups, according to their chemical structure and clinical importance: androgens, estrogens, and progesterone; glycoproteins, such as the Luteinizing Hormone (LH), Follicle Sti-

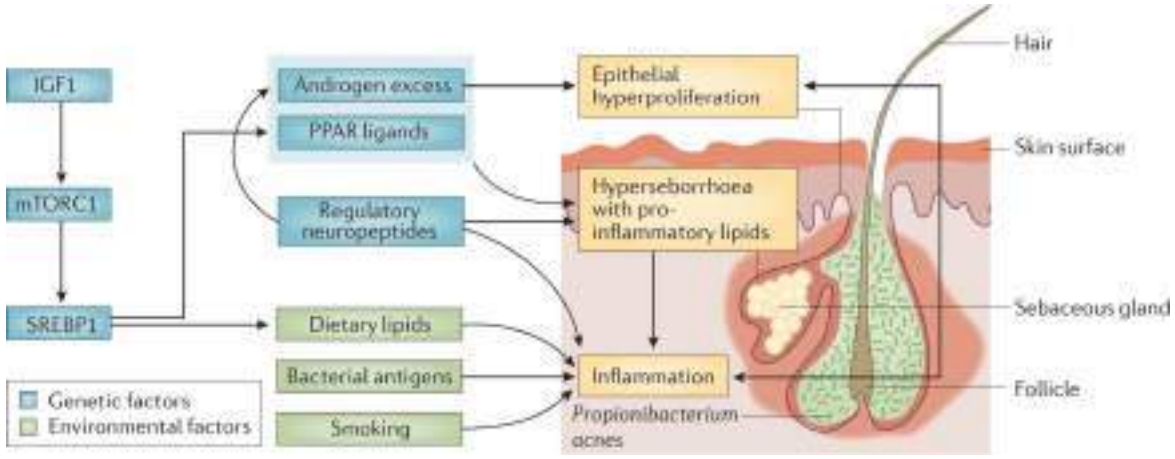

Image 1: Scheme of the 4 fundamental events for the development of acne. Extracted from Zouboulis.[5]

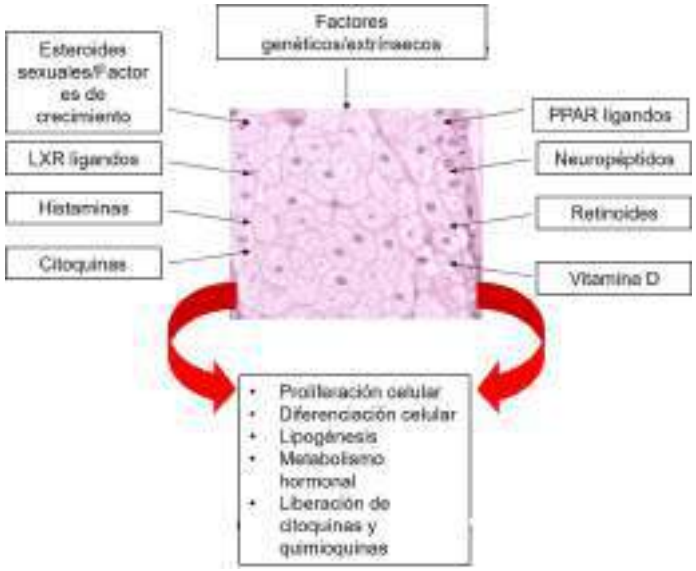

Image 2: Regulation of the biological function of the sebaceous glands. Extracted from Zouboulis.[5]

mulating Hormone (FSH), Gonadotropin-releasing hormone (GnRH) and Human Chorionic Gonadotropin (HCG); as well as peptide hormones, such as Prolactin (PRL) and Oxytocin. Androgen synthesis in the skin occurs mostly within the sebaceous glands. In the canonical pathway of androgen synthesis, testosterone originates from dehydroepiandrosterone (DHEA) and androstenedione in the gonads, as well as in the skin. Acne is a classic example of an androgen-mediated skin disease. Sebaceous glands are fully equipped with all the necessary enzymes for the synthesis and metabolism of androgens.[6]

Androgens play a crucial role in the development of acne, and although recognized as important, there are other factors involved in the formation of inflammatory acne lesions, including the adhesion of keratinocytes, the presence of propionibacterium acnes and inflammatory mediators.[7] A study conducted by Held et al. in 1984 demonstrated high serum testosterone levels in women with acne resistant to conventional treatment. It was also noted that women with the highest levels of testosterone manifested both acne and hirsutism. Moreover, the study revealed an increase of testosterone in women suffering from menstrual cycle alterations in

the absence of acne and hirsutism. They concluded that since hyperandrogenism is associated with ovarian dysfunction, the presence of acne should alert physicians to the possibility of alterations, along with systemic and fertility repercussions.[8] Marynick et al. reported an increase in dehydroepiandrosterone sulfate (DHEA-S) and testosterone among women with cystic acne.[9]

The importance of androgens in the physiopathology of acne is evidenced by clinical and observational studies. Most androgens are synthesized in the gonads and adrenal glands. However, as previously mentioned, they can also originate locally from the sebaceous glands, through the adrenal precursor DHEA-S. The main androgens that act via androgen receptors are testosterone and dihydrotestosterone (DHT). These are found in the basement membrane of the sebaceous glands and in the outer root sheath of keratinocytes from hair follicles. Although the role of androgens on the development of acne is not yet fully elucidated, there is clinical evidence to support it. The development of prepubertal acne has been associated with elevated levels of DHEA-S (precursor of Testosterone). Patients with androgen insensitivity syndrome lack functional androgen receptors and do not produce sebum. Therefore, they do not develop acne. Androgen secreting ovarian or adrenal tumors are frequently associated with acne. DHEA-S or testosterone administration increases the size and secretion of sebaceous glands. Severe acne is usually associated with elevated androgen levels.[10]

DHEA-S is the major adrenal precursor that circulates at relatively high concentrations in the blood stream. 3β Hydroxysteroid Dehydrogenase (3β-HSD) is an enzyme which catalyzes the conversion of DHEA-S into androstenedione. This may occur in the adrenal glands and in tissues, such as the sebaceous glands, with presence of 3β-HSD; androstenedione is then converted to testosterone (more potent androgen) via 17β-HSD. DHT is generated by reduction of testosterone by 5-alpha reductase. Activity of its type 1 isozyme is concentrated in sebaceous glands. The activity of 5α-reductase and 17β-HSD depends on the location of the sebaceous glands, which predominates in those located in acne-prone skin.[11,12]

Another hormone associated with the pathophysiology of acne is the growth hormone (GH), responsible for stimulating the production of insulin-like growth factor 1 (IGF-1), which may be produced in sebaceous glands and stimulate their growth. In addition, in conditions where there is an increase of GH, such as acromegaly, there is also sebum surplus resulting in the development of acne. In some tissues, androgens mediate the actions of IGF-1, influencing its effect on the sebaceous glands.[13] In cultured sebocytes, IGF-1 regulates the proliferation of keratinocytes and induces lipogenesis. Another crucial hormonal factor of acne is hyperinsulinemia, which is associated with the development of acne due to its androgenic effect on sebum production. In addition, sebum production increases under the effects of IGF-1. It is not only stimulated by androgens.[1,14]

While hormones play a major role in the progression of acne, evidently, most acne patients do not suffer from endocrine alterations. Consequently, hyperandrogenism is suspected on women with severe acne, in cases of sudden onset, when it is associated with hirsutism or menstrual cycle alterations. Furthermore, hyperandrogenism clinically presents with cushingoid features, androgenic alopecia, increased libido, acanthosis nigricans and a thick voice. Patients with hyperandrogenism may also present with insulin-resistance and are at risk of developing diabetes and cardiovascular disease. As a consequence, it is extremely important to identify patients with hyperandrogenism so that they can receive adequate treatment.[15,16] Therefore, it is very important to carry out a good physical examination and ask for medical history in order to diagnose endocrine disorder.

Consequently, what tests should we request in a case of acne from a patient suspected of having an endocrinopathy? One of the most frequent pathologies associated with acne is Polycystic Ovarian Syndrome (PCOS), which is highly prevalent in women of childbearing

age and is associated with hyperandrogenism, hyperinsulinemia, insulin resistance, ovarian dysfunction, overweight and/or obesity. Therefore, these cases require a metabolic profile, including a lipid panel, glycemia and insulinemic indexes, androgens (free testosterone, DHEA-S and androstenedione), FSH and LH. Moreover, these should be taken during the early follicular phase (FFT), between the 2nd and 5th day of the menstruation cycle, so long as the patient does not use contraceptives. If that is not the case, they may need to be stopped three months before hormonal evaluation. To confirm the diagnosis of PCOS, apart from an ultrasound measurement of the ovarian volume, the Androgen Excess and European Society of Human Reproduction and Embryology (ESHRE), requires the following criteria to be met: clinical and/or biochemical hyperandrogenism, alteration of menstrual cycles with ovulatory dysfunction and/or polycystic ovaries (more than 20 follicles per ovary or ovarian volume greater than 10 ml). Furthermore, other causes of hyperandrogenism need to be ruled out.[17,18,19,20] A study conducted by Eden reported that 74% of women with acne had PCOS,[21] and Franik et al. diagnosed PCOS in 18.2% of women with moderate/severe acne, associating the severity of acne with high levels of Testosterone and DHEAS. No association with androstenedione was found.[22] Mickael et al. found that 37.5% of PCOS patients had adult acne and emphasized that all adult women with acne should be evaluated for PCOS.[23,24]

Other endocrine pathologies associated with acne are the HAIR-AN syndrome, which consists of hyperandrogenism, insulin resistance and acanthosis nigricans and is considered a subtype of PCOS in adolescent women. It is believed to be caused by a genetic factor or autoantibodies to insulin receptors. Moreover, there is Congenital Adrenal Hyperplasia (CAH), which refers to a group of genetic disorders of adrenal steroideogenesis, associated with alterations in the enzyme activity. This article also highlights non-classical or late-onset CAH, characterized by hyperandrogenism and a clinical picture similar to that of PCOS. Its diagnosis is confirmed through androgen and 17 OH-progesterone testing. Cushing syndrome has florid symptoms and characteristic clinical signs, so it is very rare to identify acne as the reason for initial consultation. However, it presents symptoms similar to PCOS, that are secondary to hyperandrogenism, since hypercortisolism inhibits synthesis of LH and FSH. Diagnosis is confirmed though nighttime salivary cortisol and urinary free cortisol testing, as well as Nugent and ACTH testing and imaging according to etiology.[25]

Two common pathologies that must also be ruled out are hypothyroidism and hyperprolactinemia. Hypothyroidism is a disorder resulting from deficiency of the thyroid hormone. This condition, commonly autoimmune, affects the reproductive system, causing women to suffer from menstrual alterations, anovulation and infertility, due to hyperandrogenism caused by lower levels of the Sex Hormone Binding Globulin (SHBG). Moreover, there is an increase in Prolactin (PRL) and LH caused by higher levels of the Thyroid Stimulating Hormone (TSH) and metabolic alterations, such as insulin resistance and dyslipidemia. Therefore, it is also suggested to request TSH and antibody testing in case of family history or other autoimmune pathologies.[26,27] As for hyperprolactinemia, this can be caused by physiological factors, stress, medication, hypothyroidism and pituitary tumors. Effects include reproductive dysfunction, since it inhibits GnRH and gonadotropin secretion, altering gonadal steroideogenesis.

Furthermore, ovarian folliculogenesis is blocked and aromatase (enzyme which transforms androgens into estrogens) is inhibited. This leads to hypoestrogenism and anovulation. Measurement of PRL in FFT is suggested. As a further matter, since prolactin is very susceptible, rest is recommened the day before. It is also recommended not to engage in physical activity, sexual intercourse or stimuli and marijuana smoking. The patient should consult the physician about daily medication as well. These are all activities that can interfere with laboratory results.[28,29]

CONCLUSION

Based on all the aforementioned diagnostic possibilities of endocrine pathologies, whose first sign may be the presence of acne, proper evaluation is of utmost importance, including doing a thorough medical history and physical examination of patients. Furthermore, it is important to request testing and make a good differential diagnosis to optimize costs and time and to avoid erroneous diagnoses, sub-diagnoses, therapeutic mistakes, unnecessary expenses, or overmedication. These can affect the quality of life of patients and cause a negative impact on their social life and health in the short and long term. (Table 1)

Thyroid evaluation	- TSH ONLY INITIAL EVALUATION - If there is family medical history or any associated autoimmune diseases (Eg. Vitiligo), order Thyroid Peroxidase Antibody (TPO) testing. - Only if TSH is altered, order Free Thyroxine (FT4) testing.
If there is evidence of acne, alopecia, or hyperandrogenism is suspected	- Order the following between the 2nd and 5th day of menstruation: TSH, PRL, 17-OH Progesterone, FSH, LH, Free Testosterone, Androstenedione, DHEAS. - If the patient presents with amenorrhea or oligomenorrhea, order the aforementioned testing without having to wait for menstruation. - If PCOS is suspected, order also ultrasound measurement of the ovarian volume (with transvaginal ultrasound between the 2nd and 5th day of menstruation). - If the patient is taking contraceptives, suspend intake at least 3 months prior to evaluation.
If the patient suffers from acanthosis nigricans or obesity	- Order glycemia, insulin testing, lipid profile.

Table 1: Endocrinological Evaluation.

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