IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 5 Ver. 9 (May. 2018), PP 21-24
www.iosrjournals.org

Cutaneous hyperandrogenism

[1]Dr Shrivastava S B, [2]Dr Sagar Vivek, [3]Dr Singh Jasmeet, [4]Dr Gaur Diksha
[1]Consultant Dermatologist and Ex Head, Department of Dermatology, Dr Baba Saheb Ambedkar Medical College and Hospital, Rohini, Delhi)
[2]Dermatologist and Head, Department of Dermatology, Dr Baba Saheb Ambedkar Medical College and Hospital, Rohini, Delhi)
[3, 4] Residents, Department of Dermatology, Dr Baba Saheb Ambedkar Medical College and Hospital, Rohini, Delhi
Corresponding Author: Dr Sagar Vivek

***Abstract**: Cutaneous hyperandrogenism (CHA) refers to androgen dependent cutaneous features, such as hirsutism, acne,* androgenetic alopecia, *etc. The "cutaneous hyperandrogenism" is caused by in stiu over expression of the androgenic enzymes and / or hyperresponsiveness of androgen receptors in the skin. It may be primary or secondary. Primary or idiopathic cutaneous hyperandrogenism is characterized by clinical expression without hyperandrogenemia and associated androgenic conditions, whereas secondary cutaneous hyperandrogenism is characterized by clinical expression secondary to hyperandrogenemia and / or underlying androgenic conditions. Hirsutism, acne and androgenetic alopecia are considered the classical features of CHA. Polycystic ovary syndrome (PCOS) is the most common cause of secondary cutaneous hyperandrogenism, and the Rotterdam criteria are widely used for diagnosing PCOS. For labeling a case as primary cutaneous hyperandrogenism / idiopathic hyperandrogenism, presence of hirsutism or in absence of hirsutism, a combination of atypical acne and androgenetic alopecia, along with absence of hyperandrogenemia and associated androgenic conditions may be used. There are no clinical test to detect in situ over expression of the cutaneous androgenic enzymes and hyperresponsiveness of cutaneous androgen receptors, hence the diagnosis of primary cutaneous hyperandrogenism rests on excluding other causes of hyperandrogenism.*

***Key words:** Cutaneous Hyperandrogenism, Hyperandrogenism, Hirsuitism.*

Date of Submission: 03-05-2018 Date of acceptance: 18-05-2018

I. Introduction

Hyperandrogenism or androgen excess is a common endocrine disorder of women of reproductive-age, with a prevalence of 5-10%, and many of these patients do manifest cutaneous features. Hirsutism is present in up to 80% of patients with hyperandrogenism. Hyperandrogenism or androgen excess has been widely reported but there is paucity of reports on cutaneous hyperandrogenism. The purpose of this document is to precisely delineate the cutaneous features and investigative tools for diagnosis of cutaneous hyperandrgenism, specially for primary cutaneous hyperandrogenism so that they can be easily used and applied to practical clinical situations, encountered by dermatologist in their day to day practice.

Cutaneous hyperandrogenism (CHA) is a term which may be used to refer to androgen dependent cutaneous features, such as hirsutism, ance, androgenetic alopecia etc. It may or may not be associated with hyperandrogenemia (increased blood androgen levels) or androgenic conditions, such as polycystic ovary syndrome (PCOS), cutaneous or adrenal tumors etc., whereas secondary cutaneous hyperandrogenism is characterized by clinical expression secondary to hyperandorgenemia and / or underlying androgenic conditions. Consequently, CHA may be divided into primary or secondary. Primary or idiopathic cutaneous hyperandrogenism is characterized by clinical expression without hyperandorgenemia and associated androgenic conditions, whereas secondary cutaneous hyperandrogenism is characterized by clinical expression secondary to hyperandrogenemia and / or underlying androgenic conditions. Hyperandrogenism is a term used to describe the clinical signs related to the biological action of androgens.

II. Aeteopathogenesis

The "cutaneous hyperandrogenism" is caused by in situ over expression of the androgenic enzymes and / or hyper responsiveness of androgen receptors in the skin.[1]

Growing interest in dermato-endocrinology has established **Skin is an independent endocrine organ** and led to the identification of multiple hormones, receptors and classical steroidogenic enzymes in skin which are involved in synthesis & regulation of androgens.[2] Steroid sulfatase, 3βHSD, 17βHSD3, 5α reductase, 17βHSD2,

3α HSD and aromatase are the key regulatory enzymes expressed by sebocytes, dermal papilla cells and sweat glands, with sebocytes acting as the main regulators of local steroid activity. The first 4 of these enzymes are involved in androgen synthesis, whereas the last 3 are counter regulators and suppress local activity. [3] Testosterone and dehydrotestosterone (DHT) are the main androgens (hormones) and pilosebaceous unit is their main target. Testosterone interact with the androgen receptor (AR) found on sebaceous glands and the dermal papilla cells of the hair follicle and gets converted to DHT via 5α reductase. The latter is found in two isoforms; the 5α reductase type I, which is primarily expressed by sebocytes, and the 5α reductase type II, which is expressed in hair follicles.

Regulation of cutaneous steroidogenesis is analogous to that in gonads and adrenals. Though cutaneous steroidogenesis is modest, less than 1% of total synthesis, it is this local overproduction and increased receptor sensitivity that have been implicated in androgen-dependent dermatoses. The pilosebaceous unit is not only influenced by androgens, but contributes to and regulate cutaneous androgen production. Increased local concentrations are thought to mediate the development of hirsutism, acne and androgenetic alopecia.

The various causes of CHA are enumerated in the Table 1. PCOS has been reported to be the most common cause of hyperandrogenism.[4]

III. Clinical features of cutaneous hyperandrogenism

. Hirsutism, acne and androgenetic alopecia are considered the classical featurers of CHA**.** [5] Other cutaneous features suggestive of CHA includes seborrhea, acanthosis nigricans, hidradenitis suppurativa, skin tags, striae and follicular hyperkeratosis [Table2]. Besides, one should also look for non cutaneous features of hyperandrogenism such as irregular menstruation, infertility and signs of virilisation (masculine appearance with increased muscle mass and decreased breast size, deepening of voice, clitoral enlargement with increased libido) to rule out systemic causes of hyperandrogenism.

IV. Investigations

Ultrasound for ovaries to assess for PCOS which is the most common cause of cutaneous hyperandrogenism and estimation of testosterone to rule out assess the possibility of dreaded adrenal tumor should be undertaken in all cases of cutaneous hyperandrogenism. Further laboratory investigations should depend on the clinical features suggestive of the associated condition. For diagnosing primary cutaneous hyperandrogenism, the investigations mentioned in the Table 3 may be useful to exclude hyperandrogenemia and systemic diseases associated with hyperandrogenism, before labeling the case as primary cutaneous hyperandrogenism.

V. Diagnosis of cutaneous hyperandrogenism

1. Hirsutism, defined as excessive growth of terminal hair in women in a male-like pattern, is the most commonly used clinical diagnostic criterion of CHA. The Ferriman-Gallwey scale is used for the diagnosis of hirsutism. Hirsutism is considered to be present when the score is ≥ 8. It is frequently seen on the upper lip, chin, areola, chest, back, and lower abdomen. In the neoplastic virilizing states, hirsutism is of rapid onset, usually associated with clitoromegaly and oligomenorrhea.
2. Acne and androgenetic alopecia are other common androgenic skin changes. Girls with severe acne or acne resistant to oral and topical agents including isotretinoin, were reported to have a 40% likelihood of developing PCOS. In one study 15% of reproductive-age women with alopecia and no other signs of hyperandrogenism have hyperandrogenemia.[6] Acne & androgenetic alopecia might be observed without hirsutism in some hyperandrogenic women. However, isolated presence of acne or androgenetic alopecia is not used as a diagnostic criterion. But atypical acne should be considered a sign of hyperandrogenism that necessitates appropriate diagnostic investigation. Similarly a combination of features of cutaneous hyperandrogenism (apart from hirsutism) may be considered for labeling the case as cutaneous hyperandrogenism even in absence of hyperandrogenemia and disorders associated with hyperandrogenism.
3. For labeling a case as primary cutaneous hyperandrogenism / idiopathic hyperandrogenism, presence of hirsutism or, in absence of hirsutism, a combination of atypical acne and androgenetic alopecia, along with absence of hyperandrogenemia and associated androgenic conditions may be used.
4. There are no clinical test to detect in situ over expression of the cutaneous androgenic enzymes and hyperresponsiveness of cutaneous androgen receptors, hence the diagnosis of primary cutaneous hyperandrogenism rest on excluding other causes of hyperandrogenism.
5. Polycystic ovarian disease (PCOS) is the most common cause of cutaneous hyperandrogenism and the Rotterdam criteria is widely used for diagnosing PCOS.[7] Rotterdam criteria requires 2 out of 3 clinical indications to make the diagnosis of PCOS: 1. Oligo- or anovulation, 2. clinical and / or biochemical signs of hyperandrogenism, and 3. echo graphic polycystic ovaries (presence of 12 or more, 2- to 9-mm diameter follicles in each ovary and / or increased ovarian volume of > 10 mL). PCOS is a diagnosis of

exclusion, so that other etiologies of hyperandrogenism and anovulation, such as congenital adrenal hyperplasia, Cushing syndrome and androgen secreting tumors must be ruled out.

It may be pertinent to mention that most of our understanding of cutaeous hyperandrogenism is theoretical and more studies are needed to clarify it.

VI. Conclusion

Hirsutism, acne and androgenetic alopecia are the classical features of cutaneous hyperandrogenism. PCOS is the most common cause of secondary cutaneous hyperandrogenism and the Rotterdam criteria is widely used for diagnosing PCOS. Presence of hirsutism or, in absence of hirsutism, a combination of atypical acne and androgenetic alopecia, along with absence of hyperandrogenemia and associated androgenic conditions may be used to label the case as primary cutaneous hyperandrogenism

Table1: Causes of Cutaneous Hyperandrogenism

1. Primary cutaneous hyperandrogenism / Idiopathic cutaneous hyperandrogenism
2. Secondary cutaneous hyperandrogenism
▪ Disease of the ovaries
Polycystic ovary syndrome (PCOS)
Benign or malignant ovarian tumors
▪ Disease of the adrenal gland
Congenital adrenal hyperplasia (classical and non classical)
Benign or malignant adrenal tumors
▪ Disease of the pituitary gland
Cushing syndrome due to excessive adrenocorticotrophic hormone (ACTH)
Acromegaly (gigantism) due to excessive growth hormone and insulin-like growth factor (IGF-1)
Prolactinoma, a tumor that produces prolactin, and prolactin stimulates the adrenal gland
▪ Obesity and the metabolic syndrome – more androgens are produced by the adrenals and in the body fat in response to release of insulin and IFG-1, and less vitamin-D is produced in the skin
▪ Hyperandrogenic insulin-resistant acanthosis nigricans (HAIRAN) syndrome
▪ Hypothyroidism
▪ Androgenic medications (testosterone, anabolic steroids and recombinant human IGF-1)

In one large scale study the estimated prevalence of androgen excess disorders was: PCOS 72.1% (classic anovulatory patients 56.6%; mild ovulatory patients 15.5%); idiopathic hyperandrogenism 15.8%; idiopathic hirsutism 7.6%; 21-hydroxylase-deficient non classic adrenal hyperplasia 4.3% and androgen-secreting tumors 0.2%.[4]

Table 2: Clinical features of cutaneous hyperandrogenism

The classical features / common features / key features are:[5]
1. Hirsutism (seen in up to 80% of patients with hyperandrogenism)
2. Acne, specially the atypical acne (severe acne, treatment resistant acne, predominantly inflammatory acne on the lower face, neck, chest, and upper aspect of the back, adult onset acne, acne persisting into adult hood, acne with premenstrual flare, acne associated with menstrual irregularities)
3. Androgenetic alopecia / female pattern hair loss.
Other cutaneous features suggestive of cutaneous hyperandrogenism include:
4. Seborrhea
5. Acanthosis nigricans
6. Hidradenitis suppurativa
7. Skin tags
8. Striae
9. Follicular hyperkeratosis

Table 3: Laboratory investigations for evaluating hyperandrogenism

1. Pelvic ultrasound to rule out PCOS. (The ideal time is the first 3 days of the menstrual period).
2. Testosterone (Total and Free), SHBG (sex hormone binding globulin), **Free Androgen Index** (the latter is clinically the most useful measurement which can be calculated by the total testosterone concentration divided by the SHBG concentration and this figure multiplied by 100 - normal value is less than 5, although some labs will have different ranges). If total testosterone is > 200ng/dL or > 2.5 times of the normal upper range, exclude androgen secreting tumor (normal range: 20 – 80ng /dL).
3. 17-hydroxyprogesterone (elevated 17-hydroxyprogesterone level suggests congenital adrenal hyperplasia)
4. DHEAS (elevated DHEAS suggests an adrenal source)
5. LH (luteinising hormone), FSH (follicle stimulating hormone).
6. Anti-Müllerian Hormone (excessive ovarian production of Anti-Müllerian Hormone, secreted by growing follicles in excess, is now considered as an important feature of PCOS)
7. Oestradiol
8. Prolactin
9. 24-hour urinary free cortisol for assessing Cushing syndrome
10. Thyroid stimulating hormone (TSH), T3 and T4.
11. Fasting glucose (FG) and fasting insulin (FI). (A ratio of FG / FI of < 4.5 suggest insulin resistance)
12. Waist circumference (> 88 cm), triglyceride level (≥150 mg/dL), high-density lipoprotein cholesterol (< 50 mg/dL), blood pressure (≥130/85), and fasting glucose level (≥100 mg/dL) (presence of ≥3 of these features suggest metabolic syndrome)

References

[1]. Chen WC, Zouboulis CC**.** Hormones and the pilosebaceous unit. Dermatoendocrinol 2009;1:81-6.
[2]. Zouboulis CC. The skin as an endocrine organ. HORMONES 2004;3:9-26.
[3]. Chen WC, Thiboutot D , Zouboulis CC. Cutaneous Androgen Metabolism: Basic Research and Clinical Perspectives. J of Invest Dermatol 2002;119: 992-1007.
[4]. Carmina E, Rosato F, Jannì A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006;9:2-6.
[5]. Schmidt TH, Shinkai K. Evidence-based approach to cutaneous hyperandrogenism in women. J Am Acad Dermatol 2015;73:672-90.
[6]. Futterweit W, Dunaif A, Yeh HC, Kingsley P. The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. J Am Acad Dermatol1988;19:831-836.
[7]. Housman E, Reynolds RV. Polycystic ovary syndrome: A review for dermatologists: Part I. Diagnosis and manifestations. J Am Acad Dermatol 2014;71:847.e1-10.

Dr Shrivastava S B et al. "Cutaneous hyperandrogenism. "IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 5, 2018, pp 21-24.