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DIFFERENTIATING NON-CLASSIC ADRENAL HYPERPLASIA AND POLYCYSTIC OVARIAN SYNDROME PRESENTING WITH HIRSUTISM: A REVIEW

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ABSTRACT

Hirsutism, characterized by excessive terminal hair growth in a male-like distribution in females, affects 5–10% of women and often indicates underlying hyperandrogenism. Common causes include polycystic ovary syndrome (PCOS), non-classical congenital adrenal hyperplasia (NCAH), androgen-producing tumors, Cushing's syndrome, and certain medications. While PCOS is the most frequent etiology, NCAH, typically caused by a 21-hydroxylase deficiency, also plays a significant role. The clinical presentation varies but often includes increased terminal hair growth on the face, upper body, and abdomen. The Ferriman-Gallwey score aids in assessing severity. Diagnosis involves evaluating serum markers such as testosterone, DHEAS, 17-hydroxyprogesterone, and others, with ACTH stimulation tests and imaging for confirmation. Management strategies are etiology-specific. PCOS treatment focuses on suppressing androgen production using combined oral contraceptives (COCs) and anti-androgens like spironolactone or finasteride. Insulin sensitizers may benefit metabolic disturbances. For NCAH, glucocorticoid therapy regulates cortisol levels, reducing ACTH-driven androgen excess, and may be combined with anti-androgens or oral contraceptives. Hair removal techniques such as laser therapy or eflornithine cream address cosmetic concerns. Differentiating between PCOS and NCAH is critical for tailored treatment, minimizing mismanagement, and addressing both endocrine dysfunction and associated symptoms. A comprehensive approach improves clinical outcomes and enhances quality of life for affected individuals.

KEYWORD:- Hirsutism, Non-classic adrenal hyperplasia, Polycystic ovarian syndrome, Hyperandrogenism, 21-hydroxylase, Hyperinsulinemia.

INTRODUCTION

Hirsutism

The presence of terminal coarse hairs in a male-like distribution in females is known as hirsutism. Approximately 5–10% of women are affected. Finding the primary cause of hirsutism is crucial, but so is understanding how to suggest the best course of action based on that cause.

Etiology

In the past, hirsutism was thought to be a sign of elevated testosterone levels in females, which could be caused by an ovarian condition or by the adrenal glands producing more androgens. Polycystic ovarian syndrome (PCOS) and ovarian tumors are the ovarian causes of hyperandrogenism. Cushing's syndrome, androgen-producing tumors, and congenital adrenal hyperplasia (CAH), which is most frequently brought on by a 21-hydroxylase deficiency, are examples of adrenal causes. Another significant contributor to hirsutism is androgenic drugs. Idiopathic hirsutism (IH) may manifest in 20% of patients who have normal ovarian function and testosterone levels.

Higher terminal hair growth on the sides of the face, upper lip, chin, upper back, shoulders, sternum, and upper abdomen is typically seen in hirsuate women. A score was developed by Ferriman and Gallwey to clinically quantify hirsutism. Serum markers should be evaluated in a lab to determine the precise etiology. Testosterone, DHEAS, 17 hydroxy progesterone, prolactin, serum TSH, LH/FSH ratio, and 24-hour urine free cortisol are among the different serum markers.

Treatment includes androgen receptor blockers, 5-RA inhibitors, GNRH antagonists, biological modifiers.[1]

Adrenal hyperplasia

It is a collection of hereditary disorders that restrict the adrenal glands' ability to produce hormones. Both classical congenital adrenal hyperplasia and non-classic adrenal hyperplasia are forms of adrenal hyperplasia.

The more severe type, known as classic adrenal hyperplasia, is typically identified at birth and can be fatal for newborns. The CYP21A2 gene results in a 21-hydroxylase (21OHD) enzymatic deficiency, which lowers cortisol biosynthesis. But in some extreme situations, CYP21A2 mutations may also impact the production of aldosterone. The accumulation of 17-hydroxyprogesterone (17OHP) and other steroids that act as substrates for androgen excess is then encouraged by the elevated ACTH brought on by the absence of cortisol feedback. CAH is a genetic disorder that is recessive. Reduced cortisol synthesis and increased androgen secretion are hallmarks of clinical CAH phenotypes.[2]

Polycystic ovarian syndrome

The complicated disorder known as polycystic ovary syndrome (PCOS) is typified by small cysts on one or both ovaries, irregular menstruation, and/or elevated androgen levels. The condition may be primarily biochemical (hyperandrogenemia) or morphological (polycystic ovaries). Numerous genetic and environmental factors interact to cause PCOS, which is an oligogenic disorder. Primary abnormalities in the hypothalamic-pituitary axis, insulin secretion and action, and ovarian function are all part of the pathophysiology of PCOS. PCOS has been connected to obesity and insulin resistance, but its exact cause is unknown. Given that insulin regulates ovarian function and that excess insulin causes the ovaries to produce androgens, which can result in anovulation, the association with insulin function is to be expected. An ovarian follicular maturation arrest is a crucial indicator that an ovarian abnormality exists.[3]

Clinical features

Non-classic adrenal hyperplasia

Patients with NCAH exhibit variable clinical presentations, but all have signs and symptoms of excess androgen synthesis. Children and adolescents may present with premature pubarche (PP), hirsutism, menstrual dysfunction, severe cystic acne, male-pattern alopecia, advanced bone age, accelerated linear growth velocity, and decreased fertility.[4]

Polycystic ovarian syndrome

PCOS may present with amenorrhea, infertility, features of hyperandrogenemia (HA), signs of metabolic disturbances like insulin resistance, and dyslipidemia. It is a complex clinical presentation and is traditionally thought of as a triad of oligomenorrhea, hirsutism and obesity, and is now recognized as a heterogeneous disorder that results in overproduction of androgens, primarily from the ovary, and is associated with insulin resistance.[5]

Pathophysiology in association with hirsutism

Non-classic adrenal hyperplasia

The mutations that severely hinder cortisol production and cause the buildup of steroid intermediates close to the defective enzyme are what distinguish the virilizing variants of CAH (simple virilizing, salt-wasting, and nonclassic). Increased production of pituitary adrenocorticotrophic hormone (ACTH) and hypothalamic corticotrophin releasing hormone (CRH) results from the consequent absence of cortisol negative feedback inhibition. Reduced P450c21 activity impairs the conversion of progesterone (P4) to deoxycorticosterone and 17-hydroxyprogesterone (17-OHP) to 11-deoxycortisol. Usually, elevated levels of P4, androstenedione, and 17-OHP are detected. The syndrome's characteristic adrenal hyperplasia and possibly increased adrenocortical nodularity are also caused by the hypertrophy of the fasciculata-reticularis zone, which is another effect of excessive ACTH stimulation. Mineralocorticoid secretion is typically adequate in those with NCAH.

The change in enzyme kinetics brought on by CYP21A2 missense mutations is another mechanism that causes excessive adrenal androgen release, particularly in NCAH. Although the mutant enzyme protein is produced, its efficiency is lower than that of the wild type. Regardless of ACTH levels, the final effect is a higher precursor to product ratio. Therefore, even in the midst of heavy glucocorticoid therapy, P4 and 17-OHP levels in these patients may continue to be above normal. Furthermore, steroid responsiveness and metabolism may be impacted by genetic differences at additional loci. In conclusion, whereas P450c17's 17,20-lyase activity towards Δ4 substrates (conversion of 17-OHP to androstenedione) is not important in humans, individuals with CAH and NCAH might have more androgen excess because of a backdoor or another mechanism that produces more powerful androgens like dihydrotestosterone (DHT) from either P4 or 17-OHP. This alternate pathway involves the enzymes 3α-hydroxysteroid dehydrogenases and 5α-reductases. In NCAH, hirsutism may result from increased ovarian androgen release caused by the development of 5α-reductase in the ovaries.[6]

Polycystic ovarian syndrome

Excessive androgen release from the ovaries and/or adrenal glands is a hallmark of PCOS. Excessive ovarian androgen production is caused by both extrinsic (such as hyperinsulinemia) and intrinsic (such as altered steroidogenesis) ovarian causes. Women with PCOS have more developing follicles than normal controls, and their antral follicles prematurely grow to a size of 5 to 8 mm, which causes an excess of androgen production and hirsutism. Neuroendocrine variables, the operation of the valproate and HPO axis, insulin resistance or hyperinsulinemia, and obesity are additional causes.[7]

Diagnostic criteria

Non-classic adrenal hyperplasia

The majority of NCCAH instances are difficult to identify. Furthermore, many people maintain normal reproductive function throughout infancy and adolescence, stay asymptomatic, and only learn about

NCCAH when a family member is diagnosed and testing is conducted. A baseline non-stimulated value of 17 OHP is suggested as the screening test for NCCAH in the clinical guidelines put forth by the Endocrine Society. It is still unclear if a urine steroid profile is necessary for the final diagnosis. To get a definitive diagnosis and distinguish 21-hydroxylase deficit from other enzyme deficiencies in borderline cases, a full adrenocortical profile should be obtained following the ACTH stimulation test. To confirm 21-hydroxylase deficit and rule out alternative enzymatic abnormalities, a full steroid profile should be carried out in cases that are unclear. To rule out other causes of CAH, such as 11β-hydroxylase deficiency and, less frequently, 3β-hydroxysteroid dehydrogenase deficiency or P450 oxidoreductase deficiency, it would be helpful to include 17 OHP, cortisol, 11-deoxycorticosterone, 11-deoxycortisol, 17-OH-pregnenolone, Dehydroepiandrosterone, androstenedione in a serum steroid profile.[8]

Poly cystic ovarian syndrome

The NICHD criteria were purposefully arranged according to perceived significance. By applying these criteria, PCOS was identified as a syndrome with a primary determinant of androgen homeostasis, which in turn affected menstrual cyclicity. Polycystic ovaries on ultrasonography were found to be "suggestive" of PCOS but not always diagnostic. The "Rotterdam criteria" were designed to reframe PCOS as predominantly an ovarian dysfunction syndrome and to expand the syndrome's phenotypic expression. Fulfilling two of three diagnostic criteria suggests that PCOS can be diagnosed in the absence of androgen excess or monthly irregularity—the very conditions that were originally considered absolute requisites for the syndrome. Assessment of blood testosterone levels, other diagnostic standards such irregular menstruation, glucose tolerance, and acne and hirsutism.[9]

Management

Non-classic adrenal hyperplasia

Giving the patient enough cortisol will meet her daily needs and, as a result, taper the stimulation of the CRH-ACTH axis, which will reduce the creation of adrenal androgen. As a general rule, GCs are administered at replacement rather than pharmacological levels, and the impact of age, gender, laboratory results, patient-specific advice, and treatment objectives on glucocorticoid replacement therapy is carefully taken into account. Since hydrocortisone most closely mimics the natural hormone cortisol, it is usually used in children. However, because it requires many daily doses, it is not regarded as an appropriate treatment for teens and young females. Therefore, at the right dosages, the majority of adult endocrinologist's favor either prednisolone or dexamethasone.

Oral contraceptive therapy was associated with increased SHBG and decreased free testosterone concentrations. As would be anticipated, menstrual cyclicity was restored with oral contraceptive therapy.

Women complaining of excessive undesired hair growth or scalp hair loss (androgenic alopecia) may also be evaluated for the use of anti-androgens, such as finasteride, cyproterone acetate, or flutamide. In women with NCAH, cyproterone acetate was found to improve hirsutism more than hydrocortisone, even though there were only slight increases in testosterone and androstenedione levels.

The last option includes the laser hair removal therapy and also electrolysis is beneficial for the treatment of hirsutism.[10]

Polycystic ovarian syndrome

Treatment should be based on the amount of distress that hirsutism causes the patient. The degree of hirsutism and effectiveness of therapy may be guided by the modified Ferriman-Gallwey score. This index is a clinical method of evaluating and quantifying body hair growth in women.

Using combined oral contraceptives (COCs) to inhibit androgen excess is one medical strategy to reduce hair growth. This drug suppresses circulating follicle stimulating hormone and luteinizing hormone, which lowers androgen synthesis. It also increases the development of sex hormone binding globulin, which lowers free testosterone. Systemic anti-androgens may need to be added to COCs for moderate to severe hirsutism.

The most often used androgen blocker is spironolactone. By attaching itself to the androgen receptor and blocking the enzymes that produce androgen, it competes with dihydrotestosterone (DHT). Finasteride prevents testosterone from being converted to DHT. Although it has been used to treat hirsutism, flutamide, a nonsteroidal androgen receptor antagonist, is not advised because of the possibility of hepatotoxicity. There is no evidence that insulin-sensitizing medications, including metformin, have a clinically meaningful impact on hirsutism. Analogs of long-acting gonadotropin-releasing hormones are only used for patients who are unable to tolerate or do not react to other forms of treatment.

Eflornithine is a topical facial cream that inhibits the enzyme ornithine decarboxylase to treat hair that is already present. Improvement in hirsutism has been shown in 60% of patients after 6 months of use. Eflornithine plus laser treatment is superior to laser alone.[11,12]

CONCLUSION

Differentiation between NCAH and PCOS allows for a more tailored approach to treatment and management where misdiagnosis could lead to inadequate treatment and persistence of symptoms or incorrect management,

reducing symptom burden and addressing specific health risks associated with each condition and addresses both the endocrine abnormalities and the associated symptoms effectively.

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