Hirsutism: Diagnosis and Treatment

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Abstract

Hirsutism, which is a common clinical problem in women of reproductive age, is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions. It is the result of either androgen excess or increased sensitivity of the hair follicles to normal levels of androgens. The therapeutic options of hirsutism can be divided into systemic, topical, and dermato-cosmetic therapies. Patients should be informed that the response to systemic agents is slow, occurring over 3-6 months after therapy has begun. In this review, the diagnosis and treatment of hirsutism were summarized with update literature.

Definition

Hirsutism is defined medically as excessive terminal hair that appears in a male pattern in women [1]. The causes of hirsutism can be divided into non androgenic factors, hirsutism caused by androgen excess, and idiopathic hirsutism (IH). Non androgenic causes of hirsutism are relatively rare. Non androgenic anabolic drugs cause a generalised growth of many tissues, particularly hair, generally leading to vellus hypertrichosis and not hirsutism [2].

Prevalence

The prevalence of hirsutism is approximately 10% in most populations, with the important exception of Far-East Asian women who present hirsutism less frequently [3]. Although usually caused by relatively benign functional conditions, with the polycystic ovary syndrome leading the list of the most frequent etiologies, hirsutism may be the presenting symptom of a life-threatening tumor requiring immediate intervention. Androgenic causes are responsible in up to 80% of patients, and include polycystic ovary syndrome (PCOS), which affects about 70-80% of hirsute women [4,5]; hyperandrogenic insulin-resistant acanthosis nigricans syndrome, affecting about 3% [6]; 21-OH-deficient non classic adrenal hyperplasia in 2-8% of patients; and, very rarely, ovarian or adrenal androgen-secreting neoplasms [7]. As it is known, PCOS is the most frequent cause of hirsutism and IH takes the 2nd place [2]. IH is responsible for approximately 10-20% of all hirsutism cases [8]. It is seen more frequently in certain ethnic communities, particularly in women of Mediterranean ancestry.

Pathogenesis

The pathogenesis of IH is not fully understood. There is little information regarding the pathogenesis of IH in the literature. It has been postulated that 5α-reductase enzyme activity in hair follicles of these patients has increased significantly [9]. Thus, in hair follicles, conversion of testosterone to its more powerful and active metabolite, dihydrotestosterone (DHT) increases. Excessive hair growth may be due to the exaggerated response of hair follicles to normal androgen levels by the receptor function [10]. Almost all of the testosterone circulating in blood depends on sex hormone binding globulin (SHBG) and albumin. In addition, in most IH patients, increased levels of 3α-androstanediol glucuronid showing 5α-reductase binding globulin (SHBG) and albumin. In most IH patients, it is a result of peripheral androgen metabolism dysfunction. Recently, the paradoxically low gene expression levels of local 5α-reductase and aromatase in women with IH were found [12]. Additionally, insulin resistance occurs in nonobese patients with IH and appears to be related to android obesity [13].

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increased DHT levels due to primary increase in peripheral 5α-reductase activity. This situation is probably due to majority of DHT, produced in the skin, not being released into circulation and showing its effect locally before it is rapidly metabolized [11]. Serum DHT measurement is not a practical laboratory measurement in evaluating androgen metabolism or peripheral defects in peripheral androgen receptor/protein up-regulation.

On the other hand, serum total testosterone levels, by themselves, are not sufficient measurements to indicate hyperandrogenemia. While serum total testosterone levels are normal, a decrease in SHGB levels can lead to hyperandrogenemia through increased free testosterone, a bioactive version of testosterone.

Very high testosterone levels more than 1.5-2 times the upper limit

Figure 1: Evaluation of the female patient with excess growth of hair.

Figure 2: Ferriman-Gallwey scoring system.

Female patient presents with excess growth of hair:
check the sites for excess growth of hair

Increased growth of hair in male pattern distribution

Hirsutism

Find the cause, take complete history and do physical and systemic examination.

History of drugs prior to onset
oral contraceptives, danazol, testosterone, anabolic steriods, metoclopramide, methyldopa, phenothiazines, reserpine

If yes, stop the drug and replace it with some other drug

Evaluate the patient on follow up for the regression of hirsutism

Generalized increase in growth of hair on all body

Hypertrichosis

Features of hyperandrogenism

If yes, ask the rate of onset

Gradual onset with no virilization
Benign

If no

Rapid onset with virilization
Malignant

PCOS

testosterone-N/Inc.
testosterone-N/Inc.

DHEAS-N
cortisol-N
dHEAS-N
cortisol-N

17-OHP-N
17-OHP-N

LH/FSH-N
LH/FSH-N

CAH

testosterone-N/Inc.
testosterone-N/Inc.

DHEAS-N
cortisol-N
dHEAS-N
cortisol-N

17-OHP-N
17-OHP-N

LH/FSH-N
LH/FSH-N

Ovarian tumour

testosterone-N/Inc.
testosterone-N/Inc.

DHEAS-N
cortisol-N
dHEAS-N
cortisol-N

17-OHP-N
17-OHP-N

LH/FSH-N
LH/FSH-N

Adrenal tumour

testosterone-Inc.
testosterone-Inc.

cortisol-Inc.
cortisol-Inc.

17-OHP-N
17-OHP-N

LH/FSH-N
LH/FSH-N
of normal or a history of rapid development of virilisation are more likely to be associated with tumour associated hyperandrogenism. This would then trigger measurement of dehydroepiandrosterone sulfate (DHEAS) and androstenedione to identify an adrenal or ovarian source of the hyperandrogenaemia, respectively [17]. In some patients with hirsutism, functional hyperandrogenism with hidden ovary or adrenal origin can be discovered by gonadotropin-releasing hormone (GnRH) stimulation test and corticotropin (ACTH) stimulation test [17].

Thyroid dysfunction and hyperprolactinemia should be excluded by serum TSH and PRL measurements. During the early follicular phase, 21-hydroxylase deficiency and non-classical adrenal hyperplasia should be excluded through the measurement of 17-OH-progesterone level and ACTH stimulation test. In these patients, exogen androgen use should also be investigated. In summary, IH is a diagnosis of exclusion. In these cases, ovulatory dysfunction, hyperandrogenemia and other undefined states of excess androgen should be eliminated [11].

Ultrasoundographic examination of the ovaries, the adrenal glands, or both is a useful screening procedure if the symptoms suggest the presence of a neoplasm. Pelvic ultrasound may also be useful if PCOS is suspected to fulfil the Rotterdam criteria for its diagnosis.

Table 1: Medications used in treatment of hirsutism.

<table>
<thead>
<tr>
<th>Drug Dosage Treatment Schedule</th>
<th>Androgen suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives 30-50 μg/day One tablet per day for 21 days followed by 7-day pill-free interval</td>
<td>Gn-RH agonist 7/5 mg monthly A combination with 25-50 μg transdermal estradiol or 35 μg (Leuprolide acetate) intramuscularly ethinyl estradiol</td>
</tr>
<tr>
<td>Spironolactone 50-200 mg/day Continuously</td>
<td>Cyproterone acetate (CA) Induction: 50-100 mg By mouth at bedtime. Maintenance: 5 mg Cycle days 5-14 (or 15) (combination with estrogens needed in women with uterus) also available as a combination oral contraceptive pill: 2 mg CA + 35 μg ethinyl estradiol</td>
</tr>
<tr>
<td>Flutamide 62.5-500 mg/day Continuously</td>
<td>Finasteride 1-5 mg/day Continuously</td>
</tr>
<tr>
<td>Bicalutamide 25 mg/day Continuously</td>
<td>Drosipirenone (DRSP) 3 mg Available only as a combination oral contraceptive pill: 3 mg DRSP + 30 μg ethinyl estradiol or 3 mg DRSP + 20 μg ethinyl estradiol</td>
</tr>
</tbody>
</table>

Androgen suppression

Oral contraceptive (OC) agents are considered to be the first-line therapy for hirsutism in premenopausal women [19]. This treatment option has the advantage of regulating the menstrual cycle and providing contraception. Oral contraceptive pills commonly contain ethinyl estradiol (EE), in combination with a progestin. The most androgenic progestins are norgestrel and levonorgestrel, whereas the least androgenic progestins are norgestimate and desogestrel. Other progestins, such as cyproterone acetate and drospirenone, work as androgen receptor antagonists. The recommended OC includes a combination of EE with either 2 mg of cyproterone acetate or 3 mg drospirenone. In a recent prospective randomized trial, low-dose ethinyl estradiol (0.02 mg) plus drospirenone 24/4 combined oral contraceptive and ethinyl estradiol (0.03 mg) plus drospirenone 21/7 combined oral contraceptive have comparable effects in the treatment of hirsutism and were well-tolerated [20]. The mechanisms by which OCs improve hirsutism include the suppression of luteinizing hormone secretion, resulting in the inhibition of ovarian androgen biosynthesis, stimulation of sex hormone binding globulin production (effectively decreasing serum free androgen concentrations), and a mild reduction in adrenal androgen synthesis. OCs should not be prescribed to women with a history of venous thrombosis.

Spironolactone (SPA): This drug is an aldosterone antagonist as well as an androgen receptor antagonist [21]. It is a dose-dependent and competitive androgen receptor inhibitor. It also inhibits 5α-reductase enzyme activity and adrenal androgen biosynthesis. Daily effective dose vary between 50-200 mg. A recent Cochrane review of trials comparing spironolactone 100 mg/d with placebo showed a significant subjective improvement in hair growth (odds ratio 7.18, 95% confidence interval [CI] 1.96 to 26.28). The Ferriman–Gallwey score, however, did not validate these findings (weighted mean difference 7.20, 95% CI -10.98 to -3.42) [22]. Spironolactone is generally well tolerated with few side-effects, such as menorrhagia, lethargy and stomach upset. A clinically significant hypotension and increased serum potassium levels are rare if spironolactone has been used at doses of 100 mg/day. In the first months of treatment, measurements of blood pressure and serum potassium levels every 4 weeks are recommended. Spironolactone should not be prescribed to patients with renal insufficiency or hyperkalemia. As spironolactone usually causes feminization of the male fetus as well as menstrual alterations, it is best to add oral contraceptive pills.

Cyproterone acetate (CA): Cyproterone acetate (CA) is a powerful progestin with antiandrogenic activity that interferes with the binding of dihydrotestosterone to the androgen receptor and inhibits the secretion of gonadotropin, thereby reducing ovarian and adrenal androgen production. CA (2 mg) combined with EE has been shown to be more effective than placebo, but not better than other antiandrogens [23]. In the treatment of
hirsutism, CA, 100 mg/day + EE, 30-35 Kg/day combination is as effective as the SPA, 100 mg/day + OCC combination [24]. When small doses of CA, such as 2 mg/day, are combined with 35 Kg/day or 50 Kg/day of EE, it can be used as OCC. Loss of libido can be listed as one of the side effects of CA. Adrenal insufficiency is a rare complication. During the treatment, appropriate contraception should be used since the drug can cause feminization in the male fetus.

Finasteride: Finasteride is a potent inhibitor of the type 2 isoenzyme of 5α-reductase, which blocks the conversion of testosterone to 5α-dihydrotestosterone. Finasteride has been shown to lower hirsutism scores by 30%-60% in addition to reducing the average hair diameter [25]. In comparative studies, finasteride demonstrated efficacy similar to that of other antiandrogens with fewer adverse effects [26]. Other trials suggested that spironolactone and flutamide were more effective than finasteride [27,28]. In women with hirsutism, finasteride is used in doses of 2.5-7.5 mg/d. Doses of 2.5 mg and 5 mg seem to be equally effective [29]. Since the drug may lead to ambiguous genital in the male fetus, an effective contraception during its use is necessary in all women of reproductive age.

Drospirenone: Drospirenone, a progestine found in OCC, is also an antiandrogen receptor blocker. Studies have shown that drospirenone 250-500 mg/d is more effective than finasteride and triptorelin, a long acting gonadotropin-releasing hormone antagonist [30,31]. A systematic review and meta-analysis of randomized controlled trials assessing the efficacy of different antiandrogens for the treatment of hirsutism reported that when compared with metformin, drospirenone reduced the hirsutism score by 5 (95% CI 3.0-7.0; I² = 0%). Spironolactone reduced the score by 1.3 (95% CI 0.03-2.6) [32]. Due to its propensity for severe hepatotoxicity, which is occasionally fatal, flutamide should not be used as first-line therapy for hirsutism. Bicalutamide is a new, powerful and nonsteroidal pure antiandrogen drug. Its half-life is 7-10 days. It was developed in prostate cancer treatment at a 50 mg/day dose [6]. Low dose bicalutamide (25 mg/day) was shown to be effective in the treatment of hirsutism related to IH and PCOS [33]. It does not have any significant side effects and lead to irregular periods. However, hepatotoxic effects may develop at a dose of 50 mg/day.

Other treatment modalities

Insulin-Sensitizing drugs: Metformin lowers hepatic glucose production and decreases insulin levels. Thiazolidinediones (rosiglitazone and pioglitazone) sensitize end organs to insulin through their action on the peroxisome-proliferator-activated receptor-α. Meta-analyses of randomized controlled trials of insulin sensitizers for the treatment of hirsutism concluded that insulin sensitizers provide limited or no improvement for women with hirsutism [35].

GnRH agonists: GnRH agonists suppress luteinizing hormone, and to a lesser degree follicle stimulating hormone secretion, leading to a decline in ovarian androgen production. GnRH agonist therapy seems to have no therapeutic advantage over OC and antiandrogens [36,37]. As GnRH agonist therapy is expensive, requires injections, and estrogen needs to be added to the therapy, its use should be reserved for severe forms of hyperandrogenemia, such as patients with ovarian hyperthecosis who have a suboptimal response to OCs and antiandrogens.

Gluocorticoids: Gluocorticoids can be prescribed to women who: have hirsutism that is due to nonclassic congenital adrenal hyperplasia, have a suboptimal response to OCs and/or antiandrogens, exhibit poor tolerance to OCs, are seeking ovulation induction.

N-Acetyl-cysteine (NAC): NAC is commonly used as a safe mucolytic drug that has an antioxidant and insulin regulatory effect in women with PCOS [38]. Metformin and NAC appear to have comparable effects on hyperandrogenism, hyperinsulinaemia and menstrual irregularity in women with PCOS [39]. In this study, NAC significantly decreased the hirsutism score.

Topical treatment: Eflornithine hydrochloride cream 13.9 % (Vaniqa®, Skin Medica) has been approved by the US FDA for the reduction of unwanted facial hair in women. Noticeable results take about 6-8 weeks. Adverse effects include itching and skin dryness.

Cosmetic and physical measures in control and treatment of hirsutism

In treatment of hirsutism, mechanical control, removing, or destroying of unwanted hair is generally considered as a complementary treatment to drug therapy.

Shaving: Hair removal (plucking, depilation) and bleaching. Plucking or shaving of hair on the face and other parts of the body is a commonly used, but temporary method used by many women. Shaving is a commonly employed method of minimizing hair on the legs and axillae.

Electrolysis: Electrolysis (electroepilation) is a method resulting in a long-term hair damage. It is safe and effective but expensive. In this technique, a thin needle is inserted into the hair follicle, through which an electrical current is applied. There are two main types of electrolysis. Hair follicles are damaged through a chemical environment in electrolysis and through a thermal environment in thermolysis. In some cases, use of a combination of these treatments is suggested to be more effective, however, that are no clinical studies supporting this idea.

Effectiveness of repeating treatments (permanent hair loss) vary between 15-50% [40]. After the electrolysis procedure, especially if conducted by nonprofessionals, scar tissue, erythema and post-inflammatory pigment changes may occur as complications. The procedure is painful and time consuming, because the hair is treated individually. Physicians that are primarily following hirsutism patients should direct them to experienced electrolysis specialists.

Laser epilation (selective photothermolysis): Laser hair removal is one of the most effective options for reducing visible hair, however, it may not be wholly effective in all patients and combination therapy may need to be considered. Pharmacological therapy is often used in combination with mechanical hair removal due to the time needed for the drug treatment to demonstrate visible results. Clinical data investigating the use of laser treatment in combination with other treatments has focused on laser with topical eflornithine. The expert working group reviews existing data and provides guidance on the use of eflornithine in combination with laser for resistant hirsutism [41]. Permanent methods of hair reduction include photoepilation (using laser and intense pulse light [IPL] and electrolysis). Photoepilation seems to be superior to the conventional methods, such as shaving, waxing and electrolysis. A Cochrane review of photoepilation of unwanted hair growth showed that alexandrite and diode lasers are more effective, whereas little evidence was obtained for the effect from IPL, Nd:YAG, or ruby lasers [42]. However, some longer wavelength lasers (neodymium:YAG, or IPL, appear to provide benefits in patients.
who have darker skin types and therefore have less risk of burning and dyspigmentation. Paradoxical hypertrichosis is a possible, but rare, adverse effect of photoepliation, particularly in dark-skinned individuals. The basic principle of this treatment is to create direct damage to dark hair follicles [43]. Laser systems that are commonly used for the treatment of hirsutism include the ruby laser (694 nm), the diode laser (800 nm), the alexandrite laser (755 nm) and the Nd:YAG laser (1084 nm). The diode laser and alexandrite laser are considered effective in treatment of hirsutism in dark-skinned patients. The response of hairs to these laser systems is variable and not complete. In a recent study, there is no significant difference between sequential treatment with diode and alexandrite lasers versus alexandrite laser alone in the treatment of hirsutism [44]. It is still unclear whether laser treatment provides clinically significant permanent hair follicle damage. Removing hair by these means is expensive and requires multiple treatment sessions. Most patients require at least 5 to 7 sessions at least 1 month apart to permanently reduce hair growth on any single area. Hair growth is delayed when shock waves induced by thermal energy damage the germinal cells of the hair follicle [45]. Compared to electrolysis, laser treatment was shown to be a more expensive yet much less painful method that is 60 times faster. However, further new and advanced studies are necessary. Side effects of laser epilation treatment can be listed as; pigment changes in the treated skin, scars and burns in the treatment area. These side effects are minimized using today's laser technologies.

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