CONTINUING MEDICAL EDUCATION

HIRSUTISM

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Hirsutism by definition describes the quality of hair, but common usage has extended the meaning to denote a local or generalised excess of hair.[1] Body hair is of two types, (1) fine non-pigmented vellus hair (facial down), and (2) coarser pigmented terminal hair (scalp, axilla). The visual impression of hairyness is produced by the coarser type. Both genetic and hormonal factors affect hair growth. In different parts of the world, cultural factors determine what is socially acceptable in terms of quality, quantity and distribution of body hair. Thus, hirsutism that is quite acceptable in one community may cause severe embarrassment or even psychological disturbance to a woman in another community. About 3% of white women between the ages of 15 and 45 years normally have hair on their upper lip, 9% on the chin and about 6% on the sides of face.[2]

Aetiology

Hirsutism is usually the result of subtle androgen excess.[3-5] If plasma levels of all androgenic hormones are measured, about 90% of hirsute women will have elevated values of one or more. Plasma testosterone is high in 40% of hirsute females. Normally, about 98% of testosterone in circulation is bound to testosterone-binding globulin (TeBG). It is however, the free fraction which is considered to be biologically active. Free testosterone in plasma is elevated in about 85% of hirsute females because of depressed TeBG levels.[6-8]

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Some women with a significant degree of hirsutism have normal ovulatory cycles and normal circulating levels of androgens. For this group the term idiopathic hirsutism is used. Probable aetiologic factor in these patients is increased 5-alpha reductase activity in the skin, leading to increased conversion of testosterone to dihydrotestosterone which is the most potent androgen.[9-13]

Clinical causes of hirsutism

Common causes include :

1. Polycystic ovarian disease
2. Attenuated forms of congenital adrenal hyperplasia
3. Idiopathic

Rare causes include :

1. Cushing's syndrome
2. Congenital adrenal hyperplasia
3. Androgen secreting tumors
4. Hypothyroidism
5. Acromegaly
6. Drugs :
   - Phenytoin
   - Diazoxide
   - Anabolic steroids

Neoplasms : A variety of adrenal and ovarian tumors produce hirsutism. Such patients often have a rapid progression of symptoms. In addition to hirsutism, there is often evidence of virilization in the form of masculine body habitus (increased muscularity and decrease in female fat depots), deepening of voice, clitoral hypertrophy etc. Additionally, there may be

a pelvic or abdominal mass and constitutional signs of malignancy. Androgen producing tumors of the adrenal cortex may manifest with Cushing's syndrome and/or marked virilization. Androgen producing tumors of the ovaries (Arrhenoblastoma, lipoid cell and hilus cell tumors, luteoma) are usually small and these may be missed on pelvic examination and at times even on laproscopy. Usually there is elevation of plasma testosterone levels to more than 200 mg/ml.[14] In the case of adrenal tumors, levels of androgenic precursors like DHEA, DHEA-S and androstenedione are considerably elevated. DHEA-S levels more than 900 μg/dl or urinary 17-KGS values more than 50 mg/24 hour is practically diagnostic of adrenal tumors.[15-16] Androgen secreting tumors, though rare should be diagnosed early to provide appropriate therapy.

Ovarian hyperandrogenism : Most cases of hirsutism result from non-neoplastic ovarian androgen over-production. The spectrum of ovarian morphology includes normal histologic characteristics, polycystic ovaries and ovarian hyperthecosis. The corresponding clinical picture is one of increasing severity of disease from uncomplicated hirsutism and minimal menstrual irregularity to frank virilization. The basic pathogenesis of this disorder remains unknown. The plasma free testosterone level is generally elevated and TeBG levels are low. Plasma LH levels may be elevated with relative FSH deficiency.[17] Diagnosis is often presumptive and is based on the discovery of a mild elevation of testosterone in a patient with hirsutism who lacks evidence of adrenal androgen excess.

Adrenal hyperandrogenism : Attenuated forms of congenital adrenal hyperplasia (CAH) may manifest pre or post pubertally with hirsutism with or without menstrual disturbances and virilization.[18-21] Clinically, these patients are indistinguishable from women with hirsutism due to other causes.[20,22] Patients having CAH due to deficiency of 11 B hydroxylase will have hypertension. Some of these patients have polycystic ovaries which may regress with glucocorticoid therapy.

Classic CAH is inherited as an autosomal recessive trait with no clinical expression in the heterozygote. Attenuated forms of CAH are considered to be allelic variants of classical CAH on the basis of hormonal and HLA linkage studies.[23] The frequency of attenuated forms of CAH among patients with simple hirsutism in different series has been 0-30%.[20,22,24-26]

Obesity : There is an intriguing relationship between obesity and androgen metabolism.[27] Obese oligomenorrhoeic women have higher testosterone levels compared to non-obese oligomenorrhoeic women.[28,29] This could be due to excessive peripheral conversion of androstenedione to testosterone or adrenal androgen over-production.

Laboratory evaluation

Laboratory evaluation of hirsutism has greatly improved in recent years. Radioimmunoassays (RIA) of plasma steroids have almost totally replaced determination of urinary steroid concentrations owing to the greater simplicity of obtaining samples and a higher degree of precision of the former method. However, measurement of plasma steroids is a more costly procedure.

The main purpose of investigations is to exclude an androgen producing tumor, a potentially life-threatening condition as the cause of hirsutism. For this purpose the most useful tests are :

(1) *Plasma testosterone :* Testosterone levels are generally more than 1 ng/ml in most adrenal and ovarian tumors. Level more than 2 ng/ml is suggestive of tumoral hyperandrogenism.[14] In patients with ovarian

hyperandrogenism testosterone level is moderately elevated, <2 ng/ml. Normal range is 0.2 to 0.9 ng/ml.

(2) *Plasma DHEA-S :* DHEA-S is almost exclusively secreted by the adrenals. Levels more than 9000 ng/ml is diagnostic of adrenal tumors. It is also useful in screening patients with CAH due to deficiency of 3 beta hydroxysteroids dehydrogenase deficiency.[15,16] In these cases plasma DHEA-S levels are between 3000-9000 ng/ml, and these values would return to normal with dexamethasone. Normal range is 800-3000 ng/ml.

(3) *Urinary 17 ketosteroids :* This is a relatively inexpensive screening test for adrenal tumors. Levels more than 50 mg/24 hours are diagnostic of adrenal tumors. Normal range is 5-12 mg/24 hours.

(4) *Urinary 17 hydroxy steroids :* This would help to exclude Cushing's disease. This is a better test than single plasma cortisol level. Normal range is 5-10 mg/24 hours.

Other tests which would help to establish aetiological diagnosis are:

17-Hydroxy progesterone : 17-Hydroxy progesterone is a precursor of both androstenedione and deoxy cortisol. It is secreted by the adrenals (2/3) and ovaries (1/3) and is sensitive to the effect of stress. Basal values are elevated in patients with 21 hydroxylase deficiency.[41] Values above normal may be observed in patients with PCO and idiopathic hirsutism.[36] Normal range is 0.3-1.6 ng/ml.

Gonadotrophins : Gonadotrophins are secreted normally in a pulsatile fashion. So, multiple samples have to be analysed to correctly interpret the basal levels of LH and FSH. Most workers suggest that the mean of 3 samples be collected at 20 minute intervals. In PCO, LH is usually elevated with an exaggerated response to LHRH, and FSH is usually low.[42] It is occasionally high in CAH and virilizing tumor of adrenals. Normal range (for the early follicular phase), LH—3-12 lu/L and FSH—2-6.6 lu/L.

Dexamethasone suppression test : Dexamethasone will not suppress androgen levels in patients with androgen producing tumours, whereas it is very effective in normalizing elevated androgen levels in patients with congenital adrenal hyperplasia. Dexamethasone 0.5 mg is given orally every 6 hours for 7 days and serum testosterone estimation is repeated on the 7th day. This test is performed for those patients who have high basal serum testosterone. Suppressibility (normalization) of serum testosterone with dexamethasone suggests the possibility of congenital adrenal hyperplasia as the cause of hyper androgenism and excludes malignancy.

ACTH stimulation test : This test is now being used extensively to detect the attenuated forms of CAH.[42] This test is performed as follows : 1 mg dexamethasone is given at bed time, and blood samples are collected at 0, 30 and 60 minutes after 25 μg of ACTH IV. The rise of 17 OHP (hydroxyprogesterone) following ACTH is calculated. Basal values should be normal and following ACTH, there should be an increase in 17 OHP to <3 ng/ml, in cases of CAH with 21 hydroxylase deficiency.

Treatment

Treatment depends on the aetiology. Surgery and/or chemotherapy would be required for tumoral hyperandrogenism. Suppression therapy with glucocorticoid is sufficient to decrease androgen levels in patients with congenital adrenal hyperplasia. Attenuated forms of congenital adrenal hyperplasia may require only a small (0.25 to 0.5 mg) bed time dose of dexamethasone. Some of these patients would require antiandrogens for the hirsutism.

Local treatment : Dark facial hair can be satisfactorily disguised by bleaching with hydrogen peroxide (20 vol percent) or a commercial

preparation. This is simple and cheap. Commercial preparations are available which remove hair by chemical degradation. This may cause skin reactions in some persons. Threading and waxing both remove hair at the roots. Waxing is best for hairs on the legs, arms, abdomen etc. All these need to be repeated periodically, the frequency varying with individual response. Electrolysis is the only way of permanently removing hair. This is expensive and time-consuming and a complete course may take over two years. Shaving is not recommended for facial hair.

Drug therapy

Glucocorticoid is one of the oldest modes of drug therapy for hirsutism.[30] But it should be reserved for those with demonstrable adrenogenital syndrome or dominant adrenal contribution to the hyperandrogenism.

Estrogen-progestin oral contraceptive agents markedly suppress ovarian steroidogenesis and may improve hirsutism.[31] Generally it is effective only in controlling hair growth to an extent that decreases the frequency of electrolysis/cosmetic therapy. A period of 6-12 months may be required before an effect is seen.

Cyproterone acetate (CPA) is an antiandrogen which also possesses progestogen, antioestrogen and antigonadotropin properties and is the most widely used drug for the treatment of hirsutism.[32-34] During the initial clinical use, CPA was prescribed with oestrogen according to the inverted sequential method of Hammerstein et al,[35] i.e. 100-200 mg of CPA from day 5 to 15 and 50 mg of ethinyl estradiol (EE) from day 5 to 25 of the menstrual cycle. EE strengthens the antigonadotropic action of CPA and is responsible for the regular withdrawal bleeding. The inverted sequential scheme was prepared because of its long duration of action due to storage in the fat tissue. This combination has the same side effects and contra-indications as estrogen-progestogen preparations. To avoid this, a combination of percutaneous estradiol 17 beta and CPA has been prepared,[36] i.e. 50 mg of CPA daily from day 9 to 25 and percutaneous oestradiol 17 beta from day 16 to 25. Improvement of acne and seborrhoea starts during the first month of therapy and usually disappears in 75-100% cases in 3 months. Action on hirsutism is slower. Improvement starts after 6-9 months and marked positive effect is observed after 12-18 months. By this time the hair growth stops in 75% of cases. The effect is as good in ovarian hyperandrogenism as in idiopathic hirsutism, but hair growth reappears within about a month after discontinuatiom of therapy. Side effects[37-41] are asthenia, weight gain and decrease in libido. Prolonged CPA administration would increase platelet aggregability and decrease fibrinolytic activity. CPA in doses of 10 mg/day for 14 days can produce adrenal atrophy in rats. In humans conflicting results have been reported.[38-41] It can induce ACTH suppression because of its intrinsic glucocorticoid properties.

Spironolactone is an aldosterone antagonist which also has antiandrogenic properties and has been used successfully for the treatment of hirsutism.[42-49] Its mode of action as an antiandrogen is complex. It increases clearance of testosterone and decreases its production.[43] This latter effect is probably the result of decreased steroidogenesis because of an inhibition of cytochrome P450.[50-51] It also interferes with androgen action at the receptor site in target tissues.[52-55] As an androgen receptor antagonist spironolactone has been reported to be more effective than cyproterone acetate and cimetidine.[56] Its dose is 100-200 mg daily in 4 divided doses. Clinical response is obvious in about 4-6 months in most patients. There is no correlation between the decrease in the androgen level and therapeutic response as judged by hair shaft diameter.[49] So some workers tend to believe that the major effect of spironolactone is related to its androgen

receptor blockade and a reduction in 5 alpha reductase activity. Adverse effects include a potential risk of hyperkelemia and menstrual irregularity.

Cimetidine, a histamine H_2 receptor antagonist has been found to have anti-androgenic activity[57-59] and is used to treat hirsute women.[60-61] The dose recommended is 300 mg five times daily. It blocks androgen action probably by inhibiting androgen receptors; because the plasma testosterone levels do not change significantly with therapy.

Ketoconazole, an antifungal agent decreases serum testosterone levels probably by direct inhibition of testosterone biosynthesis.[61] This has been used successfully in the treatment of sexual precosity in boys.[62] This could be used to treat hyperandrogenic status in females also. But relatively small doses of this drug have produced severe toxicity in some patients.[63]

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