Hirsutism

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Summary

Hirsutism is usually caused either by an increase in androgen production by the ovary or adrenal or it may be due to increased sensitivity of the hair follicle to normal amounts of circulating androgens. The diagnostic possibilities can be resolved on clinical grounds by laparoscopy and by hormone measurements. The commonest causes of this symptom are 'idiopathic hirsutism' and the polycystic ovary syndrome. Treatment is of the underlying condition or, when that is not possible, by local removal of hair or by the administration of oral contraceptives or glucocorticoids.

HIRSUTISM is a common endocrine problem. Approximately 10% of the patients not suffering from

thyroid disease or diabetes mellitus seen in an endocrine clinic have this symptom. It is important because of the distress it causes to the patient and also because it may be an indication of a serious underlying hormonal abnormality.

The metabolism of androgens

In order to understand the patho-physiological basis of hirsutism, it is necessary to have some knowledge of the formation and metabolism of androgens. Hirsuties results when these substances are present in excess, either as a result of administration or through increased endogenous production. A scheme summarizing androgen metabolism is set out in Fig. 1.

Though testosterone is the androgenic substance

FIG. 1. Biochemical mechanisms of hirsutism.

most usually recognized, it is neither unique nor the most potent masculinizing agent (Rosenfield, 1971). In the female, testosterone may be produced under pathological circumstances by the adrenal or ovary. Another androgenic substance produced by these endocrine glands is androstenedione.

Testosterone is liberated into the blood stream and taken up by such tissues as liver, lung and skin. The skin, but not the liver, can convert testosterone into a more active substance, dihydrotestosterone (Gomez and Hsia, 1968). This conversion seems necessary for maximal androgenic activity. Dihydrotestosterone in its turn may be transformed to a physiologically weaker metabolite, androstenediol (Gomez, Hsia and Frost, 1972), which compound in turn is metabolized in the liver to a water-soluble glucuronide that is excreted in the urine.

A proportion of the testosterone that is produced and excreted can be metabolized in a similar manner. It is commonly thought that estimation of the urinary 17-oxosteroid excretion provides a satisfactory index of testosterone production. However, only 25% of the daily output of this hormone is excreted in this way. In addition, only a small fraction of the urinary 17-oxosteroids comes from testosterone. As testosterone is a particularly potent androgen small changes in its production may have important clinical effects with but minimal consequences to the rate of 17-oxosteroid excretion. In other words, determinations of the urinary 17-oxosteroids provide a very insensitive way of identifying a disorder of androgen production. In view of this, 17-oxosteroid estimations are being replaced for diagnostic purposes by measurement of specific androgens in either blood or urine.

Androstenedione is a precursor of both testosterone and oestrogens; thus in the ovary if there is a block in oestrogen synthesis the metabolism of androstenedione can be diverted towards testosterone, with a consequent increased production of the latter substance. Hyperactivity of the adrenal cortex also leads to increased androstenedione secretion with increased testosterone formation both within the gland or at extraglandular sites. Another important pathway of androstenedione metabolism is represented by its conversion in the skin via testosterone to dihydrotestosterone. Indeed, it has been shown that in normal women approximately two thirds of the dihydrotestosterone originates from this source (Ito and Horton, 1970). Androstenedione can also be taken up by the liver and lungs and converted to testosterone. Although the results of local application have shown it to be a weaker androgen than testosterone, the fact that circulating androstenedione can be transformed to dihydrotestosterone gives it an important place in the economy of androgen metabolism.

The observation that the glucuronides of testosterone and androstenediol represent end products of the metabolism of testosterone and dihydrotestosterone respectively has been utilized in the study of the pathogenesis of hirsutism where the underlying mechanism has been ill understood (Mauvais-Jarvis, Charensal and Bobas-Masson, 1973).

In addition to abnormalities arising out of disorders of steroid secretion and metabolism, it has been proposed that androgenic functions may be affected by changes in sex hormone binding globulin (SHBG). (For review see Anderson, 1974.) This substance binds circulating sex hormones with a 17 β hydroxy grouping. It has been shown that a fall in SHBG capacity leads to an increase in the free testosterone in the blood and that in addition testosterone may lower SHBG levels. Thus, it has been proposed that this binding globulin may function as an amplifier of sex hormone actions (Burke and Anderson, 1972).

Clinical causes

The important conditions in which hirsutism is found are shown in Table 1. Certain aspects merit consideration in the light of information they may shed on the mechanisms of hirsutism. Adrenocortical hyperactivity leads to excessive hair; in Cushing's Syndrome, adrenal carcinoma or the adreno-genital syndrome, increased amounts of testosterone or androstenedione may be secreted. Ovarian tumours have also been shown to produce abnormal amounts of androgen. These are all rare complaints. The menopause, a racial basis and certain drugs are all readily identifiable as causes of excessive hair, although the pathogenesis of the symptom in these instances is not always clear. So-called 'idiopathic hirsutism' is common. The term is a bad one as the pathogenesis may be apparent. This condition and the polycystic ovary syndrome (PCOS) are the commonest causes of the symptom and, therefore, will be considered in some depth.

TABLE 1. Causes of hirsutism

Racial	
Menopause	
Adrenal	
	Congenital adrenal hyperplasia
	Cushing's Syndrome
	Carcinoma
Ovarian	
	Polycystic disease
	Tumours
Drugs	
	Androgens
	Corticoids
	Phenytoin
Idiopathic	

The clinical features of the polycystic ovary syndrome are listed in Table 2. The condition may present in a number of ways. For instance, apart from hirsutism there may be a grossly disordered menstrual pattern, or the patient may complain of infertility. Apart from the hair growth, there may be no physical signs to indicate the diagnosis. Confirmatory investigation consists of laparoscopy for visualization and biopsy of the ovaries or gynaecography, where the ovaries are delineated by the intraperitoneal insufflation of air, followed by radiological definition of ovarian size. In some instances, the ovaries are not enlarged or polycystic although the clinical syndrome may be identical to that usually associated with the condition. On occasion proliferation of the theca interna cells of the ovary is found. This spectrum of pathological changes and the clinical sequelae has been called the hyperthecosis syndrome (Shippel, 1955).

TABLE 2. Features of polycystic ovary syndrome

Menstrual irregularity
Infertility
Hirsutism
Large ovaries containing multiple follicular cysts
Elevated luteinizing hormone and testosterone levels in some patients
Reduced sex hormone binding globulin (SHBG) levels

Treatment of the menstrual irregularity and anovulation in polycystic ovarian disease is beyond the scope of this review. The management of the hirsutism will be considered in a later section.

Although the condition is, by definition, associated with polycystic ovaries, it seems that the chain of events might begin elsewhere. One might speculate that the hypothalamus is abnormal and therefore releases gonadotrophin-releasing hormone abnormally. This, in its turn, affects the pituitary so that the normal pattern of gonadotrophin release, with a peak in the secretion of both gonadotrophins shortly before ovulation, is disturbed (Yen, Vela and Rankin, 1970). This leads to the ovarian abnormality, with a failure of normal luteinization and an increased production of androstenedione (Short and London, 1961). This substance is secreted into the bloodstream and may be converted into testosterone and dihydrotestosterone according to the scheme presented above. The increased androgen thus formed might cause a further disturbance in the function of the hypothalamus. Indeed, it has been proposed that the underlying lesion in the polycystic ovary syndrome is either a hypothalamus that is unduly sensitive to the effect of circulating androgen, or that there is an extra-ovarian source of androgen that affects the hypothalamus. The experimental evidence supporting

these hypotheses comes from the demonstration that there is increased androstenedione production by the ovary, and that there is increased testosterone and dihydrotestosterone production in these patients. There is also evidence that the secretion of gonadotrophins is abnormal in the condition with a tendency for luteinizing hormone levels to be high and for follicle-stimulating hormone to be low. The concentrations of hormone in blood and urine do not show a mid-cycle ovulatory peak. Further evidence placing the lesion outside the ovary comes from the demonstration that giving exogenous gonadotrophin can restore the steroid pattern to normal and induce ovulation (Crooke *et al.*, 1963). Other evidence that supports a hypothalamic basis for the condition comes from the fact that clomiphene or the administration of gonadotrophin-releasing hormone can produce ovulation in patients with the PCOS (Zarate *et al.*, 1972).

The clinical diagnosis of idiopathic hirsutism is made by excluding other causes. The patient can present at any age between the menarche and menopause although it is usually closer to the former than to the latter. The complaint is of increased hirsutism. The most affected area is the face although hair over the chest, abdomen and legs is clearly embarrassing for the patient when she comes to wear a swimming costume. The threshold of hirsutism at which women complain varies enormously. Some are worried by a small and usually acceptable amount of excess hair, others can tolerate considerable hirsuties without complaining. In addition, many of the patients have a greasy skin and acne. The steroid patterns resemble those of the polycystic ovary syndrome in that a proportion of patients have elevated blood androgen levels. However, patients with idiopathic hirsutism may have normal gonadotrophins with evidence of a pre-ovulatory peak of FSH and LH and also a rise in serum progesterone levels during the luteal phase. In some instances, the cause seems to be increased adrenal production of androgens but in other cases there is evidence that the skin itself may be the site of increased androgen production, through the intradermal conversion of androstenedione or testosterone to dihydrotestosterone (Gomez and Hsia, 1968). It has been shown that there is an increase in urinary androstanediol glucuronide levels in patients suffering from idiopathic hirsutism (Mauvais-Jarvis *et al.*, 1973). Since androstanediol is a metabolite of dihydrotestosterone, and since elevated levels may be found in instances where the urine testosterone glucuronide levels are normal, it has been postulated that there is an increased intradermal formation of dihydrotestosterone. Finally, it has been shown that those suffering from either the polycystic ovary syndrome or idiopathic hirsutism may have a reduced sex hormone binding globulin capacity in the blood.

This may contribute to the hirsutism by increasing the circulating concentrations of free testosterone.

Therapy

The treatment of hirsutism can be tackled in a number of ways. If possible the underlying condition should be remedied; but if, as frequently happens, there is no way of curing the prime cause, symptomatic remedies must be used. These consist of local measures such as shaving, depilatory creams and waxes, abrasive pads and electrolysis, or a systemic approach based on hormone therapy. In this context, both corticosteroids and oral contraceptives have been used. Corticosteroids are effective in reducing the hirsutism in approximately 50% of the patients with the condition. These drugs are given to suppress the adrenal cortex. The reduction in hair growth may take 6 months or thereabouts to show. The patient should be informed of this so that she is not disappointed when there is no early improvement. The same is true of oral contraceptives, which may also take several months to exert a beneficial effect. The oestrogen component of 'the pill' increases sex hormone binding globulin (Vermeulen *et al.*, 1969), reducing the amount of circulating free testosterone and opposes the action of androgen at the cellular level. The combination with a progestogen decreases LH production and, therefore, stimulation of the ovary is reduced. Corticosteroids should be given in small doses, such as 5 mg of prednisone at night, followed by 2.5 mg in the morning, whereas the oral contraceptives should be administered on a usual cyclical regime. It has not proved possible to predict the outcome of treatment on the basis of short term testing with either dexamethasone suppression or ACTH stimulation to test adrenal responsiveness or chorionic gonadotrophin stimulation to test ovarian activity (Ettinger *et al.*, 1973) and treatment, therefore, remains empirical. One agent should be tried for at least 6 months. If it is ineffective then the other should be used. Occasionally prescribing both corticosteroid and oral contraceptive to be taken simul-

taneously has proved effective when each given singly has failed.

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