Androgenetic alopecia and current methods of treatment

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SUMMARY

Androgenetic alopecia (AGA) is a common dermatological condition affecting both men and women. In the case of men, up to 30% over the age of 30 and more than 50% over the age of 50 are affected. AGA also affects women although clinical signs are usually milder and associated with diffuse thinning of the scalp hair. AGA invariably causes serious psychological problems especially in women. By far the most promising approaches to the treatment of baldness in men are drug therapies, such as topical minoxidil and finasteride administered systemically. Mild to moderate AGA in women can be treated with antiandrogens and/or topical minoxidil with good results in many cases.

KEY WORDS

androgenetic alopecia, androgens, antiandrogens, minoxidil, finasteride, further therapy

Male androgenetic alopecia

Male androgenetic alopecia (MAGA) is the most frequent type of thinning or loss of hair in males. The condition, also known as male pattern baldness, causes hair loss as early as late adolescence. Hamilton referred to the mutual interplay of androgens, genetic and age factors in the origin of AGA and elaborated a precise method for the clinical assessment of alopecia. Hamilton´s classification was later modified by Norwood and this is still used (1).

Polygenic heredity is assumed to be the primary cause, although the male hormone testosterone plays an important role, seemingly independent of genetic predisposition. In the hair follicle cells, testosterone converts into the biologically more active metabolite, dihydrotestosterone (DHT) catalyzed by the enzyme 5-alpha reductase. This hormone binds to androgenic receptors in the hair follicle and the specific bond triggers cellular processes which reduce the anagen phase of the hair cycle. For this reason the hair passes earlier into the telogen phase and falls out. Gradually, over succeeding cycles terminal hair converts into thinner and shorter vellus hair (i.e. the retrograde phase of the cycle) and the hair follicle becomes minute. The density of the androgenic receptors in the hair follicles varies according to location and this is genetically determined. Age factors too play an important role in AGA, the first manifestation is usually appearing in the third decade. Further factors are probably involved.

In males usually symmetric fronto-parietal retrac-

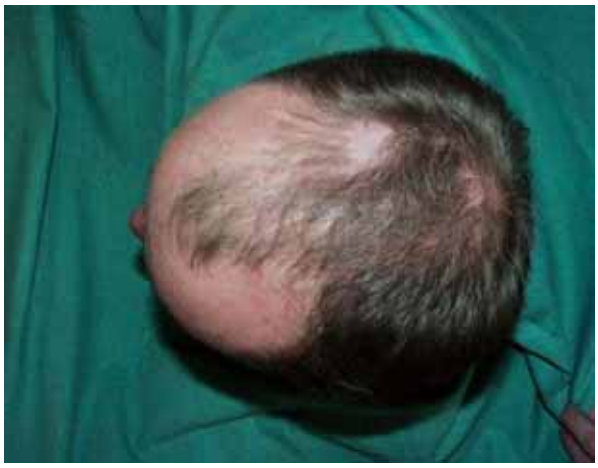

Figure 1. Androgenetic alopecia in a male.

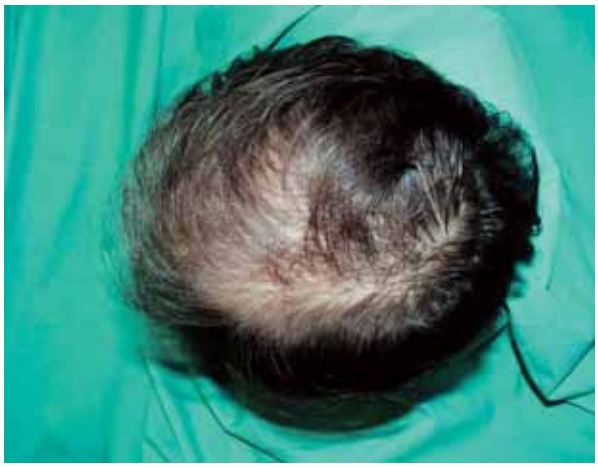

Figure 3. Androgenetic alopecia in a female.

tion of the hair-line occurs. The hair in the central part of the vertex is rarefied and thin, and the skin becomes transparent (Figure 1). The alopecia progresses and sooner or later results in a bald spot on the vertex. The remaining hair is distributed in crown-like pattern above the ears and at the scruff of the neck. However, it also becomes gradually thinner and silky, and growing more slowly.

Histological findings of the initial phase are characterized by focal perivascular basophil degeneration of connective tissue around the lower third of the anagen follicle. A perifollicular lymphocyte infiltrate then occurs. In the late stage, involution of all the structures in corium becomes apparent; the terminal hairs turn into subtle, vellus hairs, which are located higher in the dermis. The sheaths of the progressively diminishing follicles are appearing hyaline and sclerotic (2). Diagnosis of AGA in men is not difficult as the clinical picture is quite typical, especially in patients with a positive family history reporting a gradual hair loss (3). An increasing number of telogen hairs can be seen on microscopic examination. The rate of telogen hair increases primarily at the front and on the crown. Dystrophic hairs may be found less often. The increased number of telogen hairs in the peripheral areas of alopecia indicates the progressive character of the alopecia (4). The so-called phototrichogram is a non-invasive method of examination (5). It can provide data on the number of follicles (pictures taken immediately after the involved area was shaved) and the percentage of anagen and telogen hairs monitored (photos taken 72 hours after shaving) – anagen hairs are fairly well visible, while telogen look like dots (Figure 2).

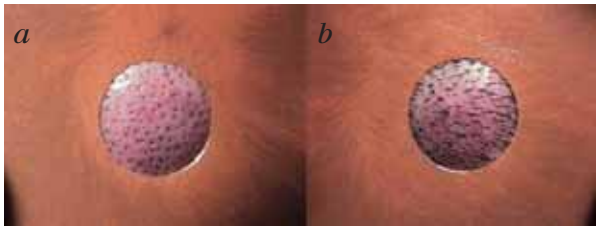

Figure 2. Phototrichograms. 72 hours after shaving: a. dots in alopecia; b. fairly visible anagen hairs.

Treatment

Topical and systemic drugs, individually or combined, may be used for the treatment. Minoxidil 2% or 5% solution is the most frequently used drug for topical application. Originally, minoxidil as a peripheral vasodilator was used in the treatment of hypertension. It was noted that systemic administration produced hypertrichosis as one of its side effects. Minoxidil has a specific direct effect on the proliferation and differentiation of follicular keratinocytes which leads to prolongation of the anagen phase. In the case of AGA, topical application is necessary twice a day over a longer period of time. However, the therapeutic effect is usually only temporary. After discontinuing the drug the hair slowly falls out again. In adddition, irritative dermatitis or contact allergic dermatitis are mentioned as adverse reactions. Minoxidil may be combined with tretinoin in 0,025% - 0,05% concentration. The preparations are administered separately, e.g. minoxidil in the morning, tretinoin in the evening or vice versa. The combination of the two pharmaceuticals results in better stimulation of hair growth. However, the risk of an irritative reaction is also higher. A derivative of minoxidil – aminexil, or the combined preparation containing *the patent RTH 16* molecule, extracted from *Ruscus aculeatus*, a phytotherapeutic agent containing ruscogenins and flavonoids. The RTH 16 molecule stimulates the production of VEGF (vascular endothelial growth factor) in the

dermal papilla. Other effective components are extracts from *Sabal serrulata* palm tree (a 5-alpha reductase blocker) and tocopheryl-nicotinate which contribute to a better blood circulation. Recently, topical antiandrogen fluridil which suppresses androgen receptors in hair follicles has been used (5,6). Owing to its lipophilic features it dissolves in the sebum. In environment containing water, it rapidly decomposes into an inactive substance. Thus, reasonable systemic tolerance and a rapid excretion of fluridil are secured (6).

Finasteride, a selective inhibitor of 5-alpha reductase of type II which reduces conversion of testosterone into DHT, is used for systemic therapy in males. It should be administered for a long period of time (a year at least), at a dosage of 1 mg per day (7). The level of DHT is reduced in the tissues as well as in the serum. The effectiveness of the drug has been demonstrated in a number of studies. The cost of the preparation however is a disadvantage. Adverse reactions such as erectile dysfunction, loss of libido, a small volume of ejaculate or gynecomastia are rather rare. The mentioned side effects are however reversible. The effect of the therapy is temporary. Similarly to minoxidil, after discontinuing the therapy, the hair loss progresses. Finasteride is more effective in the treatment of vertex type than in the treatment of the frontal type of androgenetic alopecia. Currently, clinical studies are being carried out on other inhibitors of 5-alpha reductase (e.g. dutasterid, turosterid, episterid). These represent a second generation of steroid inhibitors of 5-alpha reductase. Some also inhibit the type I isoenzyme (1).

Autotransplantation of hair may also be considered in some cases. The graft is taken from the occipital area, where the hairs are more resistant to the effects of androgens. This characteristic persists even after the follicles are transferred into the frontal or parietal areas (8).

Drugs containing vitamins, aminoacids and trace elements may be used as supportive therapy. Gene therapy may become in the future another possibility for patients with AGA. In some patients psychotherapy is recommended.

In older males, with chronic diseases it is advisable to eliminate long-term medication, which might lead to telogen effluvium and thus worsen AGA.

Female androgenetic alopecia

Androgenetic alopecia in women is less frequent. The etiology is in principle the same as in men. However, it is always necessary to exclude the possibility of endocrine dysfunction. Conversion of dehydroepiandrosterone (DHEA) into testosterone and the lack of aromatase which contributes to the conversion of androgens into estrogens are more often seen in females than in males. Apart from androgens, reduced levels of estrogens may also contribute to the incidence of AGA (hypoestrogenous AGA in women after menopause or after ovariectomy). The same may be said concerning higher levels of prolactin. Adrenal or ovarian tumors producing androgens may be a further cause.

In women with AGA the hair boundary line above the forehead is maintained, but frontally and parietally hairs are thin. The density of hair remains the same in the occipital and parietal areas (Figure 3). Exceptionally, a retraction of the fronto-parietal hair line or the formation of a bald spot (as in men) may occur after the menopause. Clinical evaluation of AGA in women uses a three-level classification according to Ludwig.

Treatment

External treatments are pharmaceuticals containing estrogens (estradiol) which prolong the anagen phase of the hair cycle and thus prevent premature hair loss. Topical therapeutic methods are similar to those used in men: minoxidil, aminexil, fluridil or a combined preparation containing RTH 16 (see above).

Hormonal contraception may also be used in the systemic treatment of AGA in childbearing women. The combination of estrogens and progestins with antiandrogen action, i.e. cyproteronacetate, chlormadinonacetate, dienogest and drospirenon should be prefered. In clinical practice the antiandrogen agents which block the DHT from binding to receptors in target tissues, reduce activity of 5-alpha reductase and decrease production of androgens in ovaria, are frequently used. The effect is rather complex as the drugs are acting on various levels. The most potent antiandrogen is cyproteronacetate, which is applied as a preparation containing 2 mg cyproteronacetate + 35 μg ethinylestradiol in fertile women (9,10,11,12). The estrogen component increases the liver production of sex hormone-binding globulin (SHBG) which reduces levels of free serum testosteron. The combination of estrogen and antiandrogen is preferred in women with androgen dependent skin anomalies (e.g. seborrhea, acne, hirsutism and androgenetic alopecia) who request contraceptives at the same time. The combination of estrogen and cyproteronacetate (1 mg cyproteronacetate + 2 mg estradiolvalerate) is used for women who lack estrogens due to natural, premature or castration menopause. During menopause it is possible to administer cyproteronacetate separately, without estrogens.

Estrogene hormones may be used in women systemically as substitution therapy, as well. They are applied when estrogen production is reduced, i.e. at the time of premenopause and during menopause. Close cooperation with a gynecologist is necessary, in these cases. The incidence of cancers may be increased after a prolonged use of estrogens, therefore preventive check-ups of breasts and genitals are recommended.

Spironolacton, which reduces the activity of 5-alpha reductase and inhibits the biosynthesis of androgens, may

be used in systemic therapy. However, among side effects are included menstrual cycle disorders and an antialdosterone effect which is manifested as reduced levels of potassium in the serum and as hypotension. Spironolacton should be used in combination with hormonal contraception in order to reduce side effects especially menstrual irregularities and prevent pregnancy in childbearing women, as it may feminize the male foetus.

Other pharmaceuticals with antiandrogen effects, i.e. ketoconazole or the non-steroid antiandrogens, cimetidine and flutamide, are not recommended owing to the high risk of adverse reactions (8,2).

Conclusions

Patients with AGA should be informed about the pathogenesis of the condition. Available medical treatments prevent progression of the disease and reverse miniaturization of hair follicles in most patients with mild to moderate androgenetic alopecia. Future success in treating AGA will require continued research on the regulation of the hair growth cycle, the development of new therapeutic approaches and well-advised use of existing drugs.

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