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An update on the treatment of female alopecia and the introduction of a potential novel therapy

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Summary

Purpose: To review treatment options for hair loss in women. *Materials and Methods:* Suggestions for treatment were based on a thorough literature search plus the present authors' experience. *Results:* There are controlled studies that support the present authors' typical treatment regimen of identifying if there are increased androgens, and if so, identify the source (ovary and/or adrenal) and then suppress with drugs, e.g., oral contraceptives or glucocorticoids. If serum androgens are normal, agents that block dihydrotestosterone at the hair shaft level, e.g., spironolactone or 5α reductase inhibitors seem to be effective. However, a recent Cochrane systematic review concludes that the only drug proven to improve alopecia by randomized controlled studies using rigorous criteria is minoxidil. *Conclusions:* The present authors will add minoxidil to their normal treatment paradigm based on this later study. The previous reasons for it was the quality of the hair produced (generally much shorter than other head hair). For alopecia related to inflammation, the present authors may have discovered a novel therapy – dextroamphetamine sulfate.

Key words: Alopecia; Female pattern hair loss; Inflammation; Dihydrotestosterone; Sympathomimetic amines.

Introduction

Female pattern hair loss (FPHL)

Female pattern hair loss (FPHL) is very common with an estimate of over 21 million women with this condition in the United States alone [1]. It is more common as women age so that it is present in 55% of women ≥ age 70, but it is present in about 10% of women between the ages of 20-30 and increases with advancing age [1].

Though increased androgens may cause FPHL, the same pattern may be observed in the presence of normal androgens. Thus the term androgenic alopecia has been changed in females to FPHL [2]. When a four-mm punch biopsy is taken from the central portion of the hair loss (preferably not temporal location), there is usually found increased numbers of miniatured hair follicles that are the type for fine short hairs known as vellus hairs. In a given area of skin there are always some terminal and vellus hairs together but normally the ratio of terminal to vellus hair is over 3:1, and in FPHL the ratio is smaller [3]. Furthermore there is a reduction in follicle depth and a greater percentage of hairs are in the telogen phase (resting) than the anagen (growing) phase [4]. The same histology is found whether the serum androgens are elevated or not [5].

From looking at the phenotype of genetic males with a 5α hydroxylase deficiency (an enzyme that converts testosterone to dihydrotestosterone, DHT) it seems clear that DHT was the more important androgen at the hair shaft level. Thus these individuals despite normal testosterone levels did not grow a beard and did not develop androgenic alopecia. Also they did not develop prostate enlargement. Therefore it was clear that DHT and not testosterone was a more potent binding hormone to the androgen receptor in the hair shaft and also the prostate. Subsequently it was discovered that there are two isoenzymes of 5α reductase and it is type II that is the one that has a greater affinity for the androgen receptor [6]. Thus if there is an increase in circulating testosterone, e.g., from polycystic ovarian syndrome or adult onset congenital adrenal hyperplasia, the increased exposure of the hair shaft to the testosterone will allow more DHT produced at the hair shaft by normal amounts of 5α reductase enzyme enzyme. This would cause hirsutism but also possibly hair loss on the head in a male pattern distribution, especially if there is also a genetic predisposition [7, 8]. However, alopecia may also develop if there are normal levels of circulating testosterone but an increase of the 5α reductase type II enzyme in the hair shaft, thus creating more DHT locally. Estrogen may compete with testosterone to inhibit 5αreductase and conversion to DHT. Thus sometimes women will develop FPHL because of estrogen deficiency as seen in post-menopausal women [9].

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There may be other factors other than androgen effect at the hair shaft level for FPHL. There was an extremely interesting case of FPHL in a genetic male but with complete testicular feminization syndrome [10]. There may be microvascular insufficiency, inflammatory conditions, or even insulin resistance itself without androgen increase an etiologic factor [11]. With insulin resistance there is an increase of insulin-like growth factor and this may stimulate more 5α reductase enzyme at the hair shaft.

In overt severe hypothyroidism progressing to myxedema, there is evidence that 57% of the women lose hair [12]. In milder cases of hypothyroidism the frequency and degree of hair loss is considerably less. The hair loss is mostly related to breakage of terminal hairs so the appearance of thinning is related mostly to areas of diminished length. The hair may get curly also. In contrast, thyrotoxicosis leads to hair that appears to be thin but it mostly related to thinner diameters of terminal hairs [12].

Alopecia areata (and totalis/universalis)

Alopecia areata is not uncommon but it occurs much less frequently (about 1.7%) in women than FPHL [13]. It tends to affect younger women than FPHL [14].

Patchy hair loss is referred to as areata, total hair loss on the head as totalis, and all body hair as universalis. The characteristic hair looks like an exclamation mark with the hair tapered proximally and wider distally.

In the acute stage hair follicles have a "swarm of bees" appearance with the hair follicles inundated with a peribulbar lymphocytic infiltrate. Autoimmunity probably plays a strong role though it may be influenced by emotional stress [15]. Generally, the younger the age of onset the worse the prognosis.

Diagnostic work-up

The typical evaluation for alopecia involves measuring, first of all, serum androgens. For women who appear to be ovulating, we measure the total and free testosterone and 17-hydroxyprogesterone in the follicular phase. A serum dehydroepiandrosterone sulfate may be obtained but it has less importance in diagnosis and treatment.

Though the free testosterone is the more clinically active androgen, for some reason in androgen increased states, e.g., polycystic ovarian syndrome with classic ultrasound appearance of ovaries and typical high LH to FSH ratio (> 1.8:1) we will frequently find the total testosterone elevated but not the free testosterone. Thus we measure both and an increase in total testosterone will lead to methods of suppressing the source of T excess production, whether it be ovary, adrenals, or both. Therapy will be subsequently discussed.

From the thyroid standpoint obvious overt hypothyroidism will be treated with thyroid hormone replacement. Subclinical hypothyroidism with a serum free thyroxin (T4) level in the normal range with a serum TSH above 2.5 microIU/mL will usually be treated with a low dose of thyroid hormone. The exception is if the free T4 is above mid-normal where we may repeat the blood test in six to eight weeks without treatment.

We look for iron deficiency but usually only treat with iron if there is an obvious iron deficiency anemia. Possibly a lack of ferritin has been hypothesized to cause hair loss by causing a shift from the anagen to the telogen phase [16, 17].

Cushing's disease is so rare that we only measure cortisol levels if there are some symptoms or signs consistent with this diagnosis.

As reproductive endocrinologists the present authors do not do scalp biopsies. However honestly, it has not been their policy to refer these patients either to dermatologists for the purpose of a biopsy.

Authors' present treatment

Increased Androgens

If the results suggest polycystic ovarian syndrome, the most common increased androgen state, an oral contraceptive is one of the first line therapies. Suppression of the increased serum LH is considered as a first line therapy because it will not only lower the elevated androgens, but also diminish the active free T by increasing sex hormone binding globulin. Furthermore the oral contraceptive will provide the necessary progesterone to prevent endometrial hyperplasia related to anovulation.

Though any oral contraceptives may be effective by lowering elevated androgens, improved efficacy may be gained by using oral contraceptive with a progestin that has less androgenic properties (all progestins in oral contraceptives are derived from androgens and have 19 instead of 21 carbon backbones). The present authors' normal preference is norgestimate, and to reduce the progestin dosage even more they prefer the ones with three graduated dosages of norgestimate as in ortho tri-cyclin®.

The present authors' experience is that monotherapy is not as effective as multiple therapies. For polycystic ovaries, they generally recommend the addition of spironolactone 100 mg twice daily to the oral contraceptive. One of the main side effects of spironolactone is to cause ovulation disturbance and irregular cycles. The oral contraceptives will generally overcome this problem. Spironolactone can reduce androgen levels without oral contraceptives so the two may be added. However, the main beneficial extra effect may be by blocking the androgen receptor thus further reducing the adversity of the remaining testosterone still circulating.

If we were to use triple therapy the next drug we would use would be a 5 alpha reductase inhibitor – finasteride or dutasteride. As mentioned they inhibit conversion of T to DHT. The one-mg dosage approved for male alopecia does not seem to be effective for women with FPHL [18]. However at five mg (the dosage used for benign prostate hypertrophy) benefits has been demonstrated [19, 20].

Dutasteride, theoretically, is more specific for the 5 alpha reductase isoenzyme most important at the hair shaft level. Dosages of 0.25 to 0.5 mg/day have shown improvement in female alopecia [21]. Since both drugs are not approved for women because if taken past 60 days of fetal life there can be feminization of the external as genitalia of a male fetus, the drugs are not generally compensated by third party payers. Since finasteride was available as a generic long before dutasteride, and thus less expensive, the present authors have mostly used five-mg finasteride. It is not clear which is more effective in these dosages. Of course the risk to a fetus is another good reason to use oral contraceptives with the 5 alpha reductase inhibitors.

Another treatment that the present authors frequently suggest is combing the hair three times per week for 15 minutes with low energy laser (Hair-Max Laser Comb). There are controlled studies showing efficacy in improving hair density [22].

The present authors have to admit that they much less commonly prescribe minoxidil. If a woman is taking it already the present authors do not stop it but they do not usually choose it as first line therapy. This reluctance is based on two concerns – one concern is that there may be the complication of facial hypertrichosis, so trading one cosmetic issue for another. Another issue is that the present authors have been under the impression that the hairs are shorter and of a different texture than the other hairs. The dosage can be two or five mg. The latter may be more effective but also more likely to cause hirsutism.

When there is increased adrenal androgens, as evidenced by an increase in serum 17-hydroxyprogesterone levels, we may add five mg prednisone or 0.5 to 0.75 mg dexamethasone before sleep (since the maximum ACTH secretion occurs during the sleeping hours). It should be recalled that there is a higher frequency of polycystic ovarian syndrome with adult onset 21-hydroxylase deficiency (or much less commonly an 11 beta hydroxylase deficiency associated with hypertension and an increase in serum 11 beta deoxycortisol) and thus glucocorticoid therapy is frequently co-treated with oral contraceptives.

Women who do not have androgen increase

All the therapies described for women with increased androgen may be used when there are normal serum androgens. Even if androgen levels are normal where an oral contraceptive would not seem as likely to be effective, it can be used to prevent menorrhagia from spironolactone or feminization of a male fetus from finasteride. For this group, estrogen replacement may be added for post-menopausal women or pre-menopausal women with estrogen deficiency.

Alopecia areata, or totalis or universalis

When faced with this condition the present authors' policy has been to inform the woman that typically the hair will regrow in time. They are told to the present authors' knowledge that topical intralesional therapies especially involving corticosteroids or immunotherapy have not been proven to be effective and can have risks. Nevertheless if they want such therapy the present authors refer them to a dermatologist who specializes in hair issues.

Other diagnostic tests and therapies based on literature review

From evaluating dermatologic literature, scalp biopsies are not that commonly employed. So the present authors do not see that test being added to their diagnostic paradigm.

The present authors have never evaluated serum zinc levels but there is some data that adding either oral zinc or a zinc lotion (zinc pyrithium) may improve hair growth through anti-inflammatory and/or antioxidant effective [23, 24].

Another lotion or shampoo that dermatologists sometimes prescribe for hair loss is caffeine based which has been claimed to increase hair membrane and tensile strength in men [25]. Because the proposed mechanism of action of caffeine is by inhibiting phosphodiesterase and to stimulate cyclic adenosine monophosphate and thus counteract the effect of testosterone at the hair follicle level, it should be effective for women also [26].

One other topical lotion for which the present authors were not aware was one-mg melatonin compounded in alcohol and glycerin [27]. Apparently it also has anti-androgenic effects at the hair follicle [28].

The present authors have already mentioned the use of minoxidil and that though they "inherit" a lot of women who are already using it on their own, they have been concerned of the side effects of hypertrichosis and not impressed by the type of hair that develops so that they generally do not add this topical therapy to their treatment regimen. However when preparing this manuscript, the present authors' literature review found a recent (2012) Cochrane systematic review that only found four studies of the various studies on treating alopecia that fulfilled the rigors of their criteria for selection of unbiased studies and all four concurred that the use of minoxidil was beneficial [29]. Pooled data for these four studies indicated a greater proportion of participants treated with minoxidil reported a moderate increase in their hair regrowth compared with placebo (relative risk 1.86) [29]. The Cochrane systematic review concluded that "single studies accounted for most of the other comparisons which were assessed as either having high risk of bias and/or they did not address the pre-specified outcome for this review and provided limited evidence of either the effectiveness or safety of these interventions. Further well designed adequately powered randomized controlled trials investigating other treatment options are still required".

For alopecia areata (and totalis and universalis) it is difficult to determine the efficacy of various topical and intralesional therapies because the condition is known for spontaneous remissions. For a discussion of these types of therapy the reader is referred to the review by Alkhalifah [30].

A novel therapy – case report

A 62-year-old woman was seeking help for alopecia of six years duration. Though it had an initial insidious start, it considerably exacerbated in the last 1.5 years. She makes note that her twin brother has a full head of hair as did her mother and her father was only mildly hair deficient. The loss of head hair was not accompanied by facial or body hirsutism but actually the opposite in that she was losing axillary hair and losing patches of pubic hair which sometimes returned.

She has been on raloxifene 60 mg/ day starting at age 47. With the notice of increasing hair loss, her gynecologist placed her on estrogen but it did not help the hair loss. The patient also lost her eyebrows totally and her eye lashes were thin. She was taking thyroid hormone for several years and her serum thyroid stimulating hormone level was normal. The clinical picture seemed to be more consistent with a type of progressive alopecia universalis, the totalis portion showing no remission but steady progressive loss, and the pubic hair behaving more in an areata fashion with remissions and exacerbations.

Close questioning found that this woman had atopic dermatitis behind the ears, and she suffered from migraine headaches and pelvic pain. The present authors explained that there is a condition that is related to hypofunction of the sympathetic nervous system that leads to a variety of pain disorders (including migraine headaches and pelvic pain) [31].

One of the main functions of the sympathetic nervous system is to control cellular permeability and hypofunction leads to the inability to filter chemicals and toxins from absorbing into tissues, thus evoking an inflammatory reaction [32]. Indeed, evidence to support this theory has been provided by the quick and effective relief of pain, e.g., migraine headaches and pelvic pain (which plagued this woman) with the sympathomimetic amine dextroamphetamine sulfate [33-37].

There is a variety of skin disorders that respond to sympathomimetic amines including eczema or atopic dermatitis [38]. Since the aforementioned patient's condition had some suspicions of alopecia, which is an inflammatory cause of hair loss, the present authors recommended the experimental use of dextroamphetamine sulfate rather than antiandrogens which they hoped would not only help the alopecia but relieve the pain from migraines, pelvic pain, and even her atopic dermatitis.

After three months of therapy with 30 mg per day of dextroamphetamine sulfate, her pelvic pain and headaches have completely disappeared along with the eczema. In addition for the first time in six years, she has shown moderate regrowth of head hair, complete restitution of body hair, and she is noticing the development of eyebrows.

Though it is possible that the hair improvement is merely related to spontaneous remission of the inflammatory state as seen in alopecia areata, the quick response in head hair despite no improvement in six years suggests that the sympathomimetic amine therapy may have been responsible for the improvement.

New considerations for diagnosis and treatment based on recent literature review

Based on relatively good safety record from minoxidil 2% twice daily for FPHL and effectiveness of at least some type of hair re-growth in the Cochrane systematic review, the present authors will consider adding topical minoxidil to their treatment paradigm [29]. However, the statement that "there is a lack of evidence for the effectiveness of some of the widely used treatments such as spironolactone, cyproterone acetate, finasteride, and laser comb therapy" will not dissuade the authors from using these therapies which they have personally observed to be reasonably effective in many but not all women. Furthermore, though there may not be enough rigor of design to satisfy the criteria set by Van Zuuren *et al.*, for inclusion in the systematic review (thus leading to the aforementioned lack of support for these therapies), there are indeed studies supporting these other aforementioned therapies and to the present authors' knowledge, no studies proving a lack of efficacy. Thus they will continue the use of spironolactone, finasteride, and laser hair comb therapy for alopecia (cyproterone acetate is not accessible in the United States).

The impressive response to the present case of alopecia, possibly of the inflammatory type, to sympathomimetic amines has to make the authors consider that perhaps other treatment refractory alopecia states may also respond to this treatment in some women. The present authors are considering using it on women where they think the problem is FPHL, but the woman does not seem to be responding to anti-androgen or estrogen therapy.

As non-dermatologists the present authors have not used very much histologic diagnosis by scalp biopsy. The two authors have decided that based on the potential novel therapy with sympathomimetic amine, it may be prudent to refer those women with apparent FPHL not responding to therapy to a dermatologist for purpose of histologic diagnosis. They may consider performing the punch biopsies ourselves. However, they would consider therapy no matter what the histologic diagnosis (FPHL or inflammatory hair loss) and then determine if dextroamphetamine sulfate is only effective in the inflammatory type or both.

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