

Diffuse hair loss in an adult female

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A case study of diffuse non-scarring alopecia in an adult female patient and an approach to diagnosis and management of female-pattern hair loss in a primary care setting

Introduction

CASE STUDY

Mrs KJ, a 29 year old manager at a busy law firm, presented to her GP complaining of recent sudden onset of hair loss over a period of a few weeks. What prompted her visit to the GP, was noticing large amounts of hair on the bathroom floor whilst on honeymoon, and subsequently that her scalp hair was suddenly thinner than usual, especially around the temporal areas. She had wondered whether she should be changed back to Cilest (from the Dianette she was currently taking), her original contraception, the cessation of which had appeared to trigger the same symptoms two years before.

On that occasion, after stopping Cilest, she had experienced amenorrhoea with facial hirsutism and similar hair loss, leading to investigations and a diagnosis of polycystic ovarian syndrome (PCOS). She then used Dianette oral contraception and for a short time, oral cyproterone acetate, which improved the hair loss. Mrs KJ, who was also a vegetarian, denied use of hair dye or chemicals on her hair, and on the day of her consultation her hair was not styled in a manner promoting traction.

Questions regarding family history revealed that her father had died of a heart attack in his fifties. The GP agreed with Mrs KJ that the hair around the temporal and crown areas appeared less than elsewhere on her scalp. The scalp was found to be otherwise normal, with no evidence of scarring

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alopecia or alopecia areata. The pull test was negative (however, her hair had been washed that morning), blood results (biochemistry and haematology) were deemed normal by the GP and because of the hair shedding, a diagnosis of telogen effluvium (secondary to stress – work and wedding planning) was made. She was advised to stay on Dianette.

Because of the previous history and treatment she was referred to a dermatologist with an interest in alopecia, who described a mixed picture of telogen effluvium secondary to low ferritin, and mild androgenetic alopecia. He also asked for the bloods to be repeated, and these showed a decreased ferritin level, high SHBG, and all the rest normal, including zinc, antibody screen, and thyroid tests. He too advised that Mrs KJ remain on the Dianette, and that she start taking an iron supplement. Of interest is that the initial ferritin level done by the GP was 37ng/l, and this fell to 28ng/l over a period of about a month. Haemoglobin was normal. Both these figures were within the normal range provided by the lab (normal range 13-150ug/l, with optimum ferritin for females advised at > 27ug/l)¹.

A few weeks after starting the iron supplements, Mrs KJ came back to see her GP to discuss work related stress which had spiked. In particular she was concerned that she would not be able to manage a very important presentation to the senior partners at the firm. She was so distressed that she found the only thing that calmed her was drinking alcohol, which she was understandably not keen on using regularly! So after some discussion about stress, the GP suggested that she try low dose propranolol for performance anxiety, for only the few days leading up to the presentation,

including the actual day of, then to discontinue. Hair loss was not discussed at this consultation.

A month later she was back to see the GP, complaining that there had been an even bigger spike in hair loss, and on contacting the dermatologist she had been advised to continue the iron supplementation. She requested a second dermatology opinion, and was then diagnosed with androgenetic alopecia secondary to PCOS, unmasked by telogen effluvium secondary to low ferritin, and a degree of scalp seborrhoea. She was advised to continue taking Dianette, iron supplementation, Ketoconazole shampoo a few times a week, topical minoxidil and topical cyproterone. She was also put on Metformin by her gynaecologist as part of the treatment for PCOS.

A number of months later there was a marked improvement in hair growth. As she was keen on starting a family, she was advised to stop oral contraception and to continue the topical treatments, but to stop both minoxidil and cyproterone once she conceived.

DISCUSSION

In order to understand abnormalities associated with hair loss, it is important to understand the normal hair physiology and anatomy.

Having personally spoken with a group of 12 GP's, about how they would approach a patient complaining of hair loss, all admitted that they felt underprepared to do so. They also admitted to a poor understanding of hair anatomy and physiology.

Hair Anatomy

Figure 1. Structure of a hair follicle²

Types of hair

There are three types of hair – terminal hairs are thick hairs found on the scalp, axilla and pubic areas; vellus hairs are finer, shorter hairs on the rest of the body; and lanugo hairs develop in utero and are shed in the first few months of life.

Anatomy

The hair starts to develop within the hair follicle, which is a stocking-like structure made up of an inner and an outer layer. The hair is divided into the part that protrudes above the skin, called the shaft, and the root, which is within the follicle.

The dermal papilla is a finger-like projection into the base of the follicle. It contains capillaries to allow for a rich blood supply to the hair bulb, forming the base of the hair root, the only living part of the hair, and therefore requires nutrients.

The hair bulb is the enlarged lower end of the hair into which the dermal papilla projects. It is made up of living cells with a high potential for division and differentiation which divide every 23-72 hours, the fastest rate of any cells in the body³. These cells are called the hair matrix. They divide and move up the follicle to become either hair cells or cells of the inner sheath of the follicle. Among the matrix cells are melanocytes which produce dark

(melanin) or red/blonde (phaeomelanin) hair pigment. Pigment is taken up by the differentiating cells of the matrix by phagocytosis. The matrix gives rise to the layers which form the hair shaft - the medulla is the inner layer(not always present in non-terminal hair), the cortex makes up the main bulk of the hair shaft and contains dead keratinocytes, and the cuticle is the layer of tightly packed overlapping cells surrounding and sealing the shaft.

The matrix is fed by the dermal papilla, which plays a significant role in hair growth. The dermal papilla produces a number of substances which have an effect on matrix cell growth and differentiation. The dermal papilla is itself under the influence of hormones and regulating substances, which include growth factors. These can increase proliferation of dermal papilla cells, which release cytokines which can act as inhibitors or stimulators of matrix cell growth.

The hair follicle is a component of the pilosebaceous unit - one of the other components being the sebaceous gland (as well as apocrine glands in specific areas such as the groin and axilla). The inner layer of the follicle extends up the shaft and ends below the opening of the gland into the follicle, while the outer sheath extends to the gland itself. The outer sheath has a fibrous membrane to which is attached the erector pili muscle, contraction of which causes the hair to stand upright (giving the effect of 'goosebumps' when someone is nervous or cold).

The sebaceous gland secretes sebum, an oily substance that helps to moisturise the skin and hair, while the apocrine gland is a sweat and scent

gland, and mostly becomes activated at puberty under the influence of hormones.

Lifecycle of the hair

There are three phases of hair growth.

Anagen – is the active phase when the cells of the hair bulb are constantly dividing and causing the hair shaft to elongate. This growth phase can last between 3-4 years.

Catagen – is the transitional or involutinal phase which follows anagen. The hair stops growing, the follicle shrinks slightly and the root is diminished and breaks away from the dermal papilla. This phase lasts 2-3 weeks.

Telogen – is the resting phase when the hair is no longer growing and the dermal papilla is not attached to the follicle. This phase lasts 6-12 weeks.

When anagen phase restarts and the follicle and dermal papilla reconnect, a new hair forms and starts growing, and can push the old hair out. About 10-15% of scalp hairs are thought to be in telogen phase at any given time. 3, 4

There is no synchronicity in the hair cycle and so small amounts, about 100 hairs per day, are lost every day, unnoticeably for the most part. Very occasionally, cycles can be synchronised, for example toward the latter part of pregnancy, thought to be under the influence of hormones, so that larger amounts at a time are shed a few months postpartum; this hair loss is by and large seen as physiological and not pathological, and normal hair growth pattern is usually soon re-established. 5

Factors influencing hair growth

Progress has been made toward understanding the processes which influence hair growth, but there is still much work to be done in this regard.

3, 6

Growth Factors

Insulin-like growth factor (IGF) accelerates hair growth depending on its concentration at the dermal papilla. This is regulated by IGF binding protein (IGFBP) which reduces the amount of free IGF available for action, and therefore has an inhibitory effect on hair growth. There are also a number of other growth factors which play in a role in hair growth regulation. 3, 6, 8

Hormones

Androgens were proven to play a role in androgenic alopecia by Hamilton who noticed that men who were castrated before puberty never grew beards or developed baldness, unless they were treated with testosterone, and that balding men who were castrated showed no progression of balding. 6

Androgens stimulate hair growth in some areas such as the beard and groin. In genetically predisposed individuals the presence of circulating androgens can also cause hair loss in areas such as the temporal and vertex areas of the scalp; the occipital area is usually spared. The reason for this is not well understood, and is thought to be related to specific receptors. 6, 8 The main androgens are testosterone and its metabolite dihydrotestosterone (DHT), the conversion occurring under the action of the enzyme 5 α -reductase at the site of the end organ, in the case of hair, the skin. DHT is more potent than testosterone in this area as it has a higher affinity for the receptors. Sex hormone binding globulin (SHBG) binds to free testosterone, preventing its

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breakdown to its more active metabolite DHT. Therefore, SHBG has an inhibitory effect on testosterone function. SHBG is in turn inhibited by IGF and insulin - these therefore help to increase the level of active testosterone and DHT. 3

Testosterone reduces the anagen phase of the terminal hair, with the result that the hair is shorter and has a smaller diameter, called miniaturisation of the hair, and conversion of the terminal pigmented hair into a vellus (often) non-pigmented hair. 3, 6, 8 The result is that with time, the areas where this occurs appears to have thinner hair growth or appear balding.

In females, androgens are manufactured in the ovaries and the adrenal glands. The ovaries produce both male and female hormones, and under the influence of insulin there is increased conversion to testosterone. 3, 9 In women with higher levels of circulating insulin, such as those with polycystic ovarian syndrome (PCOS), metabolic syndrome (MS) and insulin resistance, there can be higher levels of androgens due to increased conversion, and the suppressant effect on SHBG. 9 The net result would be a hyperandrogenic state, which could result in AGA, hirsutism, acne, voice changes, among other signs of virilisation. 7

The role of oestrogens appears to be more complicated. 15 The enzyme aromatase is found in oestrogen producing cells in the adrenals, ovaries, testes, fat cells, as well as a few other organs. Aromatase helps to convert testosterone into oestradiol, thereby decreasing the amount of free testosterone. Women who took aromatase inhibitors as part of treatment for other conditions, were found to develop androgenetic male pattern hair loss,

indicating that aromatase has a role to play in the pathogenesis of alopecia. The exact nature of this role is unclear. 10 According to Yip et al. oestrogens are at least of equal importance to androgens in scalp hair growth. 15

Minerals

While iron deficiency anaemia has been widely accepted to be a cause of hair loss¹⁷, it is less clear to what extent ferritin levels without the presence of anaemia, has on hair loss. When comparing women of child-bearing age with diffuse telogen hair loss, to those without, in the presence of no nutritional supplementation or underlying medical conditions, women with the hair loss were found to have a mean ferritin level that was significantly lower than those without hair loss. The odds that someone would have TE was higher when the ferritin level was at 30ng/ml or lower. The authors concluded that serum levels at 30ng/ml or lower therefore increased the chances of TE. 14

However Olsen et al. compared iron deficiency in women with female pattern hair loss (FPHL or AGA – difference discussed later), CTE and a control group with no hair loss, and found that while iron deficiency was common in all the women, there was no significant difference in levels between the three groups. This study cited as a limiting factor that the outcome of treating the women, who had been discovered to have iron deficiency, was unknown. 12 Theoretically then, those who had hair loss and iron deficiency, could have experienced a degree of hair regrowth after the iron deficiency had been treated. While a number of studies have supported the theory that ferritin levels affect hair loss, such as the study by Kantor et al 11 a number have also. Disputed. 12 Although the effects of ferritin on hair loss is still being

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studied and debated, Rushton suggests it would be advisable to treat even a low normal ferritin, if it was under the level of about 30-70 ng/ml; Trost et al. also advocate that ferritin above 70ng/ml should be aimed at to optimise treatment for AGA, and that the reason for the presence of anaemia or low iron stores should be sought if appropriate, while iron overload should be avoided. 13, 16

Zinc deficiency is known to play a role in alopecia, but the mechanism is unclear. 17, 18, 19 Lack of essential fatty acids can help cause a diffuse alopecia with some lightening in colour of the remaining hair. Selenium deficiency can cause a hair loss similar to zinc deficiency. Biotin deficiency can be genetic or acquired (medications like valproic acid, adult excessive consumption of raw eggs) and is also thought to play a part in causing hair loss, but there have been no clinical trials to support biotin supplementation to improve this. 19

Other factors

Hair loss is also a well known side effect of thyroid problems, inflammatory illnesses such as lupus, malnutrition, anorexia nervosa, among other conditions, all of which can be picked up as part of the differential diagnosis when evaluating someone with hair loss. 17, 20

Stress has also been known to cause hair loss, such as following major surgery or emotional trauma. 17, 20

A long list of medications also affects the hair. Heparin, Warfarin, Ace inhibitors, Beta Blockers, Allopurinol, and levodopa, among many other drugs, have been found to cause hair loss 20

Age is also an important determinant, as balding increases with age 21, as is genetics – baldness appears to run in families. There is a marked difference between races in manifestation of androgenic hair loss, with Caucasians exhibiting this the most. 8, 15

Types Of Non-Scarring Alopecia

Hair loss can be broadly classified as scarring (or cicatricial) alopecia and non-scarring alopecia. There are some occurrences when there is some overlap between these two. Non-scarring alopecia can be further divided into a diffuse hair loss, or localised/patchy hair loss (alopecia areata, not discussed further).

Diffuse hair loss

This problem is not an uncommon presenting complaint to a GP. It can be noticed by the patient as either decreased hair density/thickness, or as increased hair shedding. The main causes for this would be acute telogen effluvium (ATE), chronic telogen effluvium (CTE) and female pattern hair loss (FPHL). 17 FPHL, together with male pattern hair loss (MPHL) is also known as androgenetic alopecia (AGA), but more authors are now referring to separate nomenclature for the sexes. 8, 15, 17, 20 Although MPHL and FPHL are histologically identical the age of onset in females is later than in males. Also the patterns of hair loss between the sexes differ. The progression of the problem is not as rapid with women or as severe and there is not as good a response to anti-androgen therapy with women, as there is with men. 15, 20 Many authors have therefore suggested that in women there is therefore a very complex, multifactorial aetiology.

Female Pattern Hair Loss

This is the most common type of hair loss affecting women, with prevalence increasing with age. It affects about 12% of women aged 20-29, to about 50% of women over 40, and over 50% by the age of 80. 20, 28 FPHL is an under-recognised entity. 20

Androgenetic alopecia has been defined as progressive hair loss in genetically susceptible people in the presence of circulating androgens. Histologically, there is miniaturisation of the terminal hair follicle with progressive transformation of the terminal hair follicle (with central medulla) into a vellus hair follicle (no medulla). 15, 17, 20 The role of androgens and androgen receptors is much more established in MPHL, and therefore finasteride and minoxidil are established treatments for MPHL.

Androgens definitely have their role to play in FPHL, but there are other factors which influence the disorder as well, which are not clearly understood, such as oestrogens and iron. Many women with FPHL do not have demonstrable elevated androgen levels or other features of hyperandrogenism. 17 Women with hyperandrogenism respond better to anti-androgen treatment. 20

MPHL commonly follows the pattern described by Hamilton, with temporal recession initially, followed by vertex balding, with eventual fusion of the temporal and vertex balding areas and sparing of the occipital area). 23 In women, only a small number present with this pattern of hair loss and the degree of balding is not usually as severe as in men. 20

The pattern in FPHL follows three main distributions:

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Diffuse central-frontal hair loss with sparing of the frontal hairline. In 1977 Ludwig described this in three scales - mild, moderate and severe (almost completely bald at vertex, this is very rare). 17, 20, 24

Diffuse, mainly frontal hair loss (frontal accentuation) with breach of the frontal hairline. The Olsen scale or Christmas tree pattern - this is demonstrated by parting the hair in the midline and noting the part widening, with the narrowest part at the vertex and the widest part toward the frontal hairline. 17, 20, 24

Fronto-temporal and vertex hair thinning, in other words a male pattern of hair loss or Hamilton-Norwood- type. 17, 20, 24

Hamilton-NorwoodLudwigOlsen

(male pattern) (diffuse central)(frontal accentuation)drawing, courtesy ref. 24

More recently the Sinclair 5 point scale has been adapted and introduced, and may become more widely used as it allows more subtle description; this may become more necessary as women start to present more early with their hair loss. 20, 24

Sinclair 5-point scale for FPHL drawing courtesy ref. 24 (drawing by L. Tosti)

Because it is a progressive problem, without effective treatment the condition will worsen. However the rate of the progression is variable and unpredictable. Diagnosis is usually clinical, based on history and examination. Correct diagnosis is imperative so that the correct treatment

can be commenced to try to at least slow down/halt the progression of hair loss, or at best bring about some degree of hair regrowth. 17, 20

Progression tends to be slow, with hair loss quite diffuse. It mainly occurs in the distributions mentioned above. Miniaturised hairs are seen in the affected areas, hair shaft diversity is noted more easily on dermoscopic examination. Very occasionally peripilar halos/atrophy is seen as well. If shedding is present it is not as significant as in ATE or CTE, and the hair pull test is usually negative. Biopsy shows the abovementioned miniaturisation and a decreased terminal: vellus hair ratio, with a lower anagen: telogen ratio. The biopsy, which is not necessary unless doubt exists as to the diagnosis, should be taken from three sites, as a horizontal section and be about 4mm in diameter. 17, 20, 24 By the time a biopsy is contemplated a patient would probably be seen by a dermatologist.

While the diagnosis of FPHL is usually clinical, a biopsy should be performed when the diagnosis is uncertain. 17, 24 The main differential diagnosis is CTE. 17, 20, 23 The main difference is that CTE occurs as a rapid hair loss (FPHL is slower), lots of shedding is noted (as opposed to the presenting complaint being thinning hair). With CTE there is a positive pull test (patient should not shampoo their hair for 24 hours prior to test), when the effluvium is in an active shedding phase. Examination of the scalp in CTE does not show widening of the part, or miniaturisation, and biopsy is normal in CTE (apart from showing an increase in telogen hairs). 17, 20

Acute telogen Effluvium

ATE is also a diffuse type of hair loss which has an abrupt onset, usually seen 2-3 months after a trigger event, and usually does not last for longer than 6 months. About 15% of adult scalp hairs are in telogen phase – when telogen hairs are shed the bulb or club-shaped tip can usually be seen. Anagen hairs have a more tapered tip – there is no bulb because it is attached to the dermal papilla as the hair is still growing. 25 At the time of the precipitating event or trigger for the effluvium, as many as 75% of anagen hairs can be pushed into telogen. 20 A few months later the new anagen hairs starting to grow in the follicle push the old hairs out, and the hair shedding is noticed by the person as hair loss. In actual fact, this shedding is really a sign that new hair is growing. 25 Shedding reaches a peak and hair thickness gradually returns to normal over months – in the majority of cases things are largely back to normal by about 1 year. 17 Sometimes the precipitating event causes a corresponding Beau's line in the nail. 25 Potential causes of ATE would include: (febrile) illness, surgery, trauma/accident, childbirth, emotional trauma. Severe and sudden weight loss can also precipitate this. A number of drugs, including beta blockers, can cause an effluvium. Discontinuing the oral contraceptive can also cause hair to fall out, as can jetlag and excessive sun exposure. 25

Chronic telogen Effluvium

In CTE, the cause tends not be a single event that acts as a one-off trigger, but something that allows the hair loss to be perpetuated for longer than 6 months. 17 Many cases of CTE are idiopathic, but iron deficiency anaemia, hyper/hypothyroidism, zinc deficiency and malnutrition have been implicated

as causative/contributory factors by a number of studies. 17, 20 In CTE the hair shedding can fluctuate in severity, for example as an animal might moult. 25 Both acute and chronic telogen effluvium does not cause baldness as there is no miniaturisation or conversion of terminal hairs to vellus hairs, only decreased anagen hair growth. However, it can unmask an individual's genetic tendency to bald. 20

Treatment of Diffuse hair loss

Treatment of telogen Effluvium

Treatment of acute and chronic telogen effluvium involves treating the underlying causes, if found. Removing the trigger factor for acute telogen effluvium should allow for an improvement in hair growth in most cases by about one year; most people will see an improvement after a few months already. 17, 20 If no cause for CTE is found, a biopsy to rule out FPHL should be considered. 20 The course for CTE is that shedding occurs in phases, but never leads to balding. 20 It is thought to potentially take up to 3-10 years to resolve, but there are insufficient studies that have looked properly at this condition over time. 17 Empiric use of minoxidil 2% has been suggested, in the hope of decreasing telogen and increasing anagen. 20

Treatment of FPHL

While a general practitioner may not be expected to be able to offer all of the therapies available for the treatment of FPHL, it is very helpful to have a good understanding of the therapeutic processes so that patient questions can be dealt with in a knowledgeable manner; this improves the therapeutic

relationship. The primary care doctor should be able to initiate medical treatment in an uncomplicated case of FPHL.

Minoxidil

Minoxidil was first discovered to improve AGA while undergoing development as an oral antihypertensive drug, when it was seen to cause hypertrichosis, and hair growth in balding men. 8, 22, 26 It is now used as a topical treatment for AGA in a 2% and 5% strength. The exact mechanism of action is unclear. It is converted into its active metabolite by an enzyme present in the outer follicle of the hair sheath. In its activated form the drug opens potassium channels to bring about a vasodilatory effect, but studies looking at this effect after topical application of minoxidil, have been inconclusive. 22, 27 Other potential mechanisms of action could include induction of new blood vessel formation by increasing vascular endothelial growth factor gene expression at the site of the dermal papilla. Another theory is that it could stimulate activity of an enzyme (cytoprotective prostaglandin synthase I) which stimulates hair growth. 22, 27 It could also increase expression of the gene for hepatocyte growth factor, which stimulates hair growth. Messenger and Rundegren 2004 have proposed that the mechanism of action is to cause premature end to telogen and prolong anagen. 20, 27 Ongoing studies are needed into the mechanism of action of minoxidil, as this could help with development of better treatments.

Although not enough is known about the mechanism of action to improve alopecia, it has been proven to be efficacious for both men and women. 17, 20, 22, 23, 26, 27 The European Dermatology Forum (EDF) performed an

extensive literature review (of specific databases) with the aim of formulating evidence-based treatment guidelines for the treatment of AGA (it differentiates between male and female treatments but calls the conditions AGA). Based on the studies reviewed, it recommends topical application of minoxidil 2% or 5% applied twice daily for mild to moderate AGA, with the 5% strength favoured if greater efficacy required. A foam application (as opposed to the solution) is also available, but further studies comparing efficacy to the solution, are needed. 20 For women, the recommendation is also to use the 2% solution twice daily, but there is no evidence currently available to support the use of 5% strength in females. 20, 22, 28 In a study by Lucky et al. female patients were found to show psychosocial improvement after using 2% and 5% minoxidil respectively, compared with placebo. More pruritis, local irritation and hypertrichosis were reported by women using the 5% solution. 28

Patients should always be counselled thoroughly before starting medication. This is vital for compliance, as the progression of the hair loss is only halted/reversed for the duration of compliance. Counselling should include how to apply the medication (1ml in a dropper, applied to dry scalp morning and night and not washed for at least 4 hours – if hair/scalp get wet within an hour the medication should be reapplied), the importance of compliance for results, when to expect an improvement, as well as potential side effects. 20 There are three main side effects. One is an apparently paradoxical shedding of hairs – if minoxidil does indeed shorten telogen and stimulate anagen then any new hairs forming would ‘push out’ the old. It is very important that the patient is informed to continue with the treatment, and they could be

reassured that this is a sign of the medication working; this effect usually occurs in the first 2-8 weeks of treatment. 17, 20, 22, 23 The other main side effects are related to contact, so it is important to warn the patient to wash their hands immediately after application. Hypertrichosis can occur, mainly because of incorrect application (usually disappears about 4 months after cessation of the treatment). 17, 20, 22, 28 The patient should be advised to apply the medication 2 hours before going to bed at night so that there is less risk of transfer to the pillow, and subsequently to the face. 22 Contact dermatitis, either allergic or irritant, has also been reported. 17, 20, 22, 28 The main causative agent is the vehicle for the drug, called propyleneglycol, in higher concentration in the 5% solution. 20, 22, 28 If contact irritant dermatitis is confirmed then the vehicle should be changed (for example to the foam application – positive results have been produced by Lucky et al with regards to equal efficacy to the solution, and better tolerability from subjects). 20 However if an allergy to minoxidil is confirmed then the treatment needs to be abandoned/changed completely. 20, 22

The EDF has advised that efficacy should be assessed at 6 months for cessation of shedding and 12 months for regrowth. 22 The treatment should be continued for as long as the therapeutic benefit is required. This is lost with cessation of treatment, with hair loss recommencing about 3 months after cessation. Pregnant and lactating women are advised not use minoxidil, even though no adverse outcomes were noted after a large study. 17, 20, 22, 23

5 a-reductase inhibitors

These drugs were initially aimed at treating men with prostatic hypertrophy, and both licensed 5 α -reductase inhibitors, finasteride and dutasteride, are currently used to treat this condition. Of the two, finasteride is also registered to treat AGA in men. 22

The mechanism of action of finasteride is to act as on 5 α -reductase II, the receptors of which are mainly found in the scalp, skin and liver. Dutasteride acts on both types I (gut and prostate) and II 5 α -reductase. Finasteride reduces serum DHT by about 58-60% 17, 22 while dutasteride reduces serum DHT by about 90% 22

In all the clinical trials assessed by the European Dermatology Forum, 1mg of finasteride taken daily showed a significant improvement by 6 months, compared to placebo, and the same was true at 12 months, and up to a 60 months follow-up. Dutasteride was also looked at by a number of authors and showed an improvement in hair loss but at a much higher dose than that needed to treat benign prostatic hypertrophy. 22 Further studies comparing its efficacy to 1mg finasteride are needed.

There are not many studies assessing the efficacy of finasteride in females – in a study of post menopausal women taking finasteride, further hair loss was noted. 22, 23 Finasteride is therefore not indicated in women, although one study has shown positive results in women with FPHL and hyperandrogenism. 17, 20 There have also been sporadic reports of finasteride improving hair loss in individual female patients. 20, 23 More studies into finasteride for use in FPHL, are needed.

If finasteride is used off licence in a female of reproductive age, adequate contraception needs to be taken to avoid feminisation of a male foetus. 17, 20, 22, 23 For this reason it is completely contraindicated in pregnancy. Finasteride also lowers PSA levels, so a baseline PSA blood test should be done on men aged 45 years or older, who are starting finasteride. 20, 22, 23, 26 Finasteride also has a number of side effects which have potential psychosocial impact – it can cause erectile dysfunction in men and decreased libido. As with minoxidil, counselling is therefore indicated as compliance is important for outcome. For those who do not tolerate the 1mg dosage, a 0.2mg dosage can also be effective. 22

Studies looking at combining the above therapies were done. Khandpur et al showed that 2% minoxidil applied twice daily, and 1mg of oral finasteride daily, taken together, was superior to each therapy used by itself. Taking finasteride with Ketoconazole shampoo was also reported to be superior to the abovementioned monotherapies. 20, 29 Combination therapies can therefore be considered if monotherapies are insufficient. Compliance is of course important.

Hormone Treatment

According to the European Dermatology Forum, evidence for the efficacy of hormonal treatment is limited. Anti-androgens act by blockading androgen receptors (AR) – these are therefore contraindicated in men as they cause feminisation. There is no evidence to support the use of oestrogens in men. (ref. 22) The Forum also decided that, based on their literature review, there was insufficient evidence to support the use of oestrogens, progesterones or

anti-androgens in FPHL, although there was a place for anti-androgens in the treatment of some women with hyperandrogenism. 22 Use of Spironolactone to treat hirsutism and FPHL is common, especially in the US. 20 Spironolactone acts by binding to AR and also acts at the site of the ovary to reduce manufacture of androgens. In a study spironolactone was shown to be as effective as cyproterone acetate in FPHL, but only a small percentage of women showed improvement; the majority of women in the study showed no response. 20 Spironolactone is taken at a dosage of 100mg – 200mg per day, with concurrent use of contraception. Cyproterone acetate is taken at a dosage of 25-100mg per day for 10 days of every menstrual cycle, also with concurrent use of contraception. 17, 20 Cyproterone inhibits gonadotrophin-releasing hormone (GnRH) and blocks AR; it is also used for treatment of acne, prostate cancer and hirsutism. Vexiau compared minoxidil 2% and cyproterone – the former was more effective in women who had no hyperandrogenism, and the latter was more effective for those who had, 20, 30 suggesting some role for anti-androgens.

Flutamide is another anti-androgen; it compared favourably against finasteride and cyproterone for treatment of FPHL, and also compared favourably against Spironolactone for treatment of acne, seborrhoea, FPHL and hirsutism. 20 However, this drug has a significant side effect profile in that it can potentially cause hepatotoxicity – ongoing monitoring is therefore required and the medication should be stopped or not commenced in the face of significant abnormality. 20

Anti-androgen therapy can cause disturbances of the menstrual cycle, breast tenderness, and are contraindicated in pregnancy due to feminisation of male foetus. Spironolactone increases potassium levels, so monitoring of electrolytes is required, as well as hypotension. Adequate counselling prior to commencement of treatment is paramount. 20

Surgery

There are two types of surgical procedures used to treat alopecia – these are hair transplantation and scalp reduction surgery; they can also be used in conjunction with each other. Because AGA is pattern hair loss, as mentioned earlier, there will be certain areas on the scalp that have a greater tendency to balding than others, for example the occipital area does not have a tendency to bald in pattern hair loss. It makes sense therefore, that for hair transplantation to be effective, the donor site needs to be from an area that is less androgen sensitive or prone to shedding, such as the occipital scalp. The process involves microsurgical techniques of implanting harvested terminal hair follicles under local anaesthetic, into areas of scalp needing more hair. Donor sites must be carefully chosen, the grafts harvested, prepared and implanted without any damage, in order to obtain optimal results. Certain techniques show superiority of efficacy 22. One study showed a combination of hair transplantation surgery with 1mg of oral finasteride had superior results at one year compared with surgery alone. 22

In women the ideal candidate has thick occipital hair and decreased hair density over the frontal scalp. 20 Between one and three sessions are usually required 6 months apart to allow adequate assessment of each

surgery. 20 Occasionally there is an effluvium a few weeks after the procedure, but this can often be avoided with concurrent use of 2% minoxidil 20. The best results are achieved in controlled/stabilized AGA and when there is optimal, sufficient donor site. Women with concurrent diffuse effluvium are not good candidates as there is not an optimal donor site. In a good candidate, surgery can result in as good a result as in men. 20

Scalp reduction surgery is not as widely practiced as hair transplant surgery. In scalp reduction surgery the area of scalp with alopecia is surgically removed and two areas of scalp with hair growth are surgically approximated. Scarring and the need for revision surgery, are disadvantages. 20, 22

Supplementation

A number of trials looking at amino acid supplementation, trace element supplementation (zinc, copper, iron), vitamins like biotin and niacin, antioxidants and millet seed, were assessed by the EDF who found the most of the studies flawed in some way and therefore inconclusive. 22 An improvement in hair growth with use of a herbal treatment containing hibiscus, polygonum, fennel chamomile, thiya and menthe was reported by one author 22 Another study also showed some improvement in hair growth after application of a Chinese herbal treatment for six months. 22 Retinoids were not proven to show a significant improvement. 22 Saw Palmetto was also looked at by some studies and showed improvements that were significant when compared with placebo. 22

Cosmetic Aids

While treatments for FPHL are ongoing, or if the patient may for some reason choose not to pursue treatment, or if these were perhaps contraindicated in someone, discussing ways of coping cosmetically may be useful. One study 22 noted that both males and females suffer psychologically when afflicted with hair loss, but for men it was more socially acceptable to be balding than for women, and so the psychological impact can be higher for women who face more pressure to have a 'normal' physical appearance. Another study looked at the difference between a woman's perception of the severity of her hair loss, compared with the clinician's assessment of this 31. It found that women consistently rated the severity of their hair loss as higher than the clinician. The study also found that the decrease in quality of life was disproportionate to the degree of hair loss. 31 It is therefore important to consider the patient's psychological and mental health as well when approaching the issue of hair loss. For this reason it is important to address cosmetic aids and discuss practical issues which may help camouflage the problem in a way that makes the patient feel less conspicuous. Sinclair makes the point that a good hairstylist can be invaluable 20; styling hair in a way to create volume and hide the problem, and learning washing, drying and styling techniques that discourage damage to remaining hair is important.

Camouflaging products to create the illusion of thickness include hair building fibres, spray hair thickeners, masking lotion, and topical shading. Fibres can be shaken onto the affected scalp and works in about 30 seconds

to create the illusion of thickness. Spray thickeners also create the illusion of increased thickness but can be messy to apply. Tinted lotion and topical shading are less messy and help to create thicker looking hair. Another option, especially if the hair loss is very advanced or if the application of products is unacceptable for whatever reason, is to use hair extensions, hair weaves/integration pieces or wigs. These depend on choice, and on the quality and amount of remaining hair.²⁰ Hair accessories such as hats, scarves and other fashion accessories can also be useful.

The Hair Consultation

History

After noting gender and age, it is important to determine the nature of the complaint. Has the hair been falling out, breaking off, appearing thinner without noticeable hair loss, or does the quality of the hair appear different.²³ Conditions like monilethrix can result in short fragile hair that breaks easily; in some protein energy malnutritional states such as kwashiorkor hair also breaks easily; with thyroid disorders hair can appear dry and course.

Has the problem occurred in the past, or is this the first episode? Has it appeared to improve before? In other words, what is the course of the problem? In CTE, the problem can occur for short periods of time, intermittently for a number of years. Spontaneous regrowth occurs in TE postpartum. Is there a seasonal variation? Also determine the age at which the problem was first noted.^{23, 24}

Have there been associated symptoms related to the hair problem, such as dandruff, itching of the scalp, burning or painful sensation of the scalp, any

rashes occurring simultaneously on the body, any systemic features such as tiredness (anaemia, thyroid problems). Initial signs of AGA can be itching or trichodynia. 24 Any inflammatory condition of the scalp can cause hair loss which can be precluded by itching, scaling or flaking of the scalp. An oily skin can indicate increased activity of the seborrhoeic glands which could indicate increased androgen sensitivity/levels. 24

What is the patient's past medical history (including any change in health in the year before noticing the hair loss)– severe infections, chronic disease which can cause anaemia of chronic disorder, thyroid problems, medications taken, eczema, any autoimmune disorders, and any chemotherapy or radiation therapy in the past. 23, 24 Treatment for breast cancer involving anti-oestrogen therapy can be associated with male pattern hair loss. 10 Gynaecological history for women is also important – menorrhagia, PCOS, amenorrhoea, hormonal contraception, whether post-menopausal and if so has/is hormone replacement therapy used. Discuss past pregnancies – was there difficulty in conceiving, miscarriages, was delivery particularly stressful/complicated. Discuss future family planning. Is there a tendency toward acne, hirsutism, and scalp/skin seborrhoea/oiliness 23, 24

Mental health – issues such as trichillomania, anorexia, and taking antipsychotic or antidepressant medication.

Medications can affect hair growth – beta blockers, anti-epileptics, chemotherapy, thyroid medication, oral contraceptives. 20, 23, 24

Social history is also important – some studies have pointed at smoking exacerbating hair loss. 24 Diet can affect nutritional status, which can affect hair. Sudden weight loss can trigger hair loss. 24 Being overweight has been connected with hyperinsulinaemia and metabolic syndrome. The use of anabolic steroids can be significant. 24 Enquire about hair products and styling methods – traction can cause problems.

Family medical history can indicate an autoimmune problem, family history of male or female pattern balding, skin disorders such as atopy or psoriasis, PCOS, hirsutism. 23, 24

It is also important to note from the history how the condition has affected the patient. In the study by Reid et al. mentioned earlier, 31 the clinician's assessment of severity of hair loss did not predict the patient's perception of severity of the problem, or their quality of life. While mental health may not always be present as a causative factor, hair loss can cause psychosocial problems such as depression, loss of self esteem and social isolation. 26

It is also important to find out what the patient's expectations, and hopes, for treatment are. 23

Examination

The clinician's initial impressions are important – is the patient wearing a hairstyle with lots of traction on the scalp, is the person over/underweight, is there obvious hirsutism or acne, is the face looking a bit shiny Does the person appear emotionally distressed/shy and recalcitrant?

It is important to clinically evaluate the whole scalp, including skin and actual hair, facial skin and hair growth (are eyelashes present, is there hirsutism, is there appropriate beard growth), body skin and hair growth, and nails (in alopecia areata the nails can appear pitted). 23, 24

Scalp

With non-scarring alopecia the scalp should appear normal. Sometimes increased seborrhoea can aggravate AGA. (ref. 26) Scaling, erythema and crusting can indicate inflammation. With scarring alopecia there is loss of the follicular os. 24 Sun damage in longstanding baldness can be significant. 24 Yellow dots are seen in alopecia areata on dermoscopy, which is thought to represent follicular openings plugged with a keratinous and sebum debris mixture. This can help to distinguish FPHL and TE, from alopecia areata incognita. 32

Hair

Note the hairstyle, and whether the hair shafts appear damaged/ dry/ brittle/ broken. 23, 24 Part the hair and compare width of the parting at the vertex, frontal, temporal and occipital areas – this is important when describing pattern of hair loss. Use a sheet of white paper for dark hair, and black paper for light/grey hair, over a parting in the hair, to look for miniaturised hair, broken hairs or variations among the hairs. 33 Exclamation hairs (tapering broken hairs) indicate alopecia areata. 32 Miniaturisation indicates AGA. 32

Note the pattern of hair loss – in MPHL, there is thinning and recession bitemporally initially, then in the vertex. In FPHL the pattern can demonstrate the Ludwig, Olsen (Christmas tree pattern) or the Sinclair

description, or the Hamilton distribution. 20, 23, 24 Diffuse thinning of the hair can also be caused by diffuse alopecia areata or diffuse telogen effluvium. 20, 26, 24, 32

Pull test

This is an important test to help differentiate at the initial consultation between the types of non-scarring alopecia, when not clinically obvious. It is important to determine when hair was washed, as a head washed more recently would be more likely to have lost telogen hairs and have fewer to yield. 17, 20 About 50-60 hairs are pulled between the thumb, forefinger and middle finger. A positive test occurs when more than 10% of the hairs can be pulled out. 17, 20, 23, 24 Performing the test on different areas of the scalp is useful in excluding diffuse telogen effluvium; often this can co-exist with a pattern hair loss. 17 The test is usually negative for pattern hair loss, except when performed during a telogen phase in the affected area, when there would be more hairs than usual in the telogen phase. If the pull test is positive, a diagnosis other than pattern hair loss should at least be considered. 24

Non-scalp hair and skin

Abnormal distribution of body hair is important to note as can indicate a hormonal problem which may need further investigations. An increased amount of body hair can be hormonal or genetic or related to medication. 24 Absent sexual hair can indicate a hormonal problem, and absent or scanty eyebrows or eyelashes can be associated with alopecia areata or frontal fibrosing alopecia. 24 Acne and seborrhoea can be hormonal. 26

Nails are affected by a number of dermatoses, but of the non-scarring alopecias, only alopecia areata has been known to cause nail changes. 24
Mentioned above is that the trigger causing ATE can sometimes cause Beau's lines in the nails. 25

Lab tests

The history and clinical examination should allow a diagnosis of non-scarring alopecia to be made, and for the problem to be classified as either pattern hair loss, telogen effluvium, or alopecia areata (or a combination). Because confounding factors may also be present which can exacerbate hair loss or prevent treatment, it is reasonable to do some laboratory tests, if suggested by the findings of the history and examination. 17, 20, 23, 24

Serum ferritin and thyroid hormone levels should be done. 17, 20, 23, 24

In men it has been advised that after the age of 45, a PSA level should be performed prior to treatment with finasteride, as this drug can lower PSA. The patient should be made aware of this side effect. 23, 26

If on history and examination there is a suspicion of a virilising tumour, PCOS, or hyperandrogenism in women, then additional tests such as a free androgen index (FAI) (total testosterone x 100 / SHBG) test, and prolactin level as screening tests for hyperandrogenaemia – for example levels of FAI of 5 and above indicate that someone may have PCOS (reference). Depending on findings, FSH, or cortisol levels may also be needed, and the patient referred to either a gynaecologist or endocrinologist (or both if needed). 17, 20, 23, 24
Hormone levels are affected by ingestion of exogenous hormones so should be tested if no hormones taken for 2 months

at least, and the time of the menstrual cycle noted for adequate interpretation of hormone results. 23 Oestrogens can increase the level of SHBG, and therefore improve FAI. 23

Other investigative tools available to dermatologists are

- dermoscopy – in FPHL it shows increased hair diameter diversity and an increased number of vellus hairs. 32

Global photography – helps to evaluate the course of hair changes in clinical studies in an objective fashion – set regions of the scalp are photographed using standardised procedure and equipment 23, 24

Trichoscan – for diagnostic and follow-up purposes, it measures hair density and anagen/telogen ratios. For reproducibility tattoos of the sample areas in frontal and occipital regions are needed. 23, 24

Trichogram – to be used by a dermatologist experienced in its use. 24

Biopsy – not usually required for diagnosis of non-scarring alopecia, but may be helpful if there is doubt about the diagnosis. Much more relevant for cases of scarring alopecia. 17, 20, 23, 24

CASE DISCUSSION AND CONCLUSION

The case of Mrs KJ is interesting because of the complexities involved.

Her initial hair loss had occurred on cessation of Cilest. She therefore believed that stopping this had caused the problem, and helped maintain hair thickness, hence her request to be put back on Cilest when she saw her GP. As mentioned above, cessation of the combined oral contraceptive has been noted to cause transitory hair loss. However, at the time of the initial

presentation she was put on Dianette and cyproterone as she was found to have PCOS. This is one of the potential causes of hyperandrogenism. Although her blood results did not show any hormonal imbalances, she mentioned that she had had facial hirsutism at the time, so was clinically hyperandrogenous without being biochemically hyperandrogenous. It may be that in the presence of normal hormone levels, she was more responsive to existing hormones, possibly with increased receptor sensitivity. The blood results could also not accurately be relied on as she was not taken off the oral contraception. The fact that there was hair growth with cyproterone suggests that androgens had their role to play in her case.

When she presented to the GP for the second time, there were a number of issues to note. She had a very stressful and demanding job. It must be noted that Mrs KJ's personality was that of a perfectionist, and it could be argued that people like this, who are driven to succeed might be more susceptible to stress. She had also planned her wedding and honeymoon in the months leading up to the dramatic hair shedding which occurred whilst on honeymoon. Added to this was her vegetarian diet, and although she was not anaemic, her ferritin level was below 'the optimum' levels discussed above, even though normal according to the lab reference range.

The plot thickens. Based on the above the GP had correctly made the diagnosis of a telogen effluvium. However Mrs KJ had the compounding problem of PCOS. The underlying problem for Mrs KJ was the PCOS, a syndrome affecting about 5-10% of women. 34 PCOS symptoms are related to abnormal levels of sex hormones – high/high-normal Luteinising Hormone

(LH) and androgens (including testosterone), and low Follicle Stimulating Hormone (FSH) and progesterone. The cause for PCOS is not known but there is an association with insulin resistance. 35 Insulin resistance causes the body to increase the amount of insulin produced. Higher insulin levels increase ovarian production of androgens, which inhibit ovarian follicular maturation, hence the menstrual abnormalities. 35 Higher androgen production also has an effect on hair growth, specifically, thinning of scalp hair in a pattern of hair loss.

Although there was no history of baldness in the family, male or female, she presented with a typical male pattern of baldness with bilateral thinning of the temporal areas (Hamilton I). The second dermatologist noted increased seborrhoea, which can indicate clinical hyperandrogenism, and treated with Ketoconazole. This bitemporal thinning could have been occurring unnoticed as FPHL tends to be slowly progressive. Her hair loss shot to her attention with the abrupt onset of the telogen effluvium.

One more interesting point to note is that when she saw her GP to discuss stress, neither considered the impact of the propranolol on her hair loss. She did present a few weeks after the short period of having used the propranolol, with a sudden increase in her hair loss, which may well have contributed to by the beta blocker. Whether a few days at a low dose would have made such an impact, is uncertain. The interesting case of Mrs KJ serves as a perfect example of why primary care physicians need to have a good approach to dealing with the rather complex problem of diffuse hair loss.

Once each of the (potential) contributory factors had been treated, Mrs KJ started to grow a thicker, more dense, head of hair.

Lastly, there is a small subset of patients in whom non-scarring hair loss serves to uncover more serious medical problems such as thyroid disease, hyperinsulinaemia, PCOS, Metabolic Syndrome and potential for heart disease. This link has been the subject of numerous studies. Matilainen et al. investigated whether early AGA could serve as a marker for insulin resistance, and concluded that further research was needed, but suggested that people with early AGA could benefit from cardiovascular screening. 36 This was supported by Arias-Santiago et al. who investigated lipid levels in women with AGA, and found that women with AGA were shown to have significantly higher levels than women with no AGA. 37 Abdel Fattah and Darwish found that people with metabolic syndrome, regardless of the presence of AGA, were more likely to have insulin resistance, compared with people with AGA and normal controls. 38 This serves to highlight the point that while much work is still needed to clarify the above, the vigilant GP, presented with the problem of FPHL, should also be on the lookout for comorbid disease or potential for these. Mrs KJ's father had died of a heart attack in his early fifties, but she maintained a healthy lifestyle, normal lipid and glucose profile, and low-normal blood pressure and so had a low risk for cardiovascular disease.

There is much on hair loss that was not discussed in this paper, such as cicatricial or scarring alopecia, localised hair loss (alopecia areata) and hair loss in children and adolescents. If the latter occurs, and appears to be non-

scarring, it is best discussed with a paediatric endocrinologist and dermatologist.

Dr Yumnah Ras

MBChB, June 2011

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