Fortnightly review: Male pattern androgenetic alopecia
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Androgenetic alopecia is characterised by progressive, patterned hair loss from the scalp. Recently the pathogenesis and genetic basis of the hair loss have been better understood, as has the distress experienced by men who have lost their hair. There have also been breakthroughs in the treatment of androgenetic alopecia.

The transition of some terminal hairs into vellus hairs is a universal physiological secondary sexual characteristic. Androgenetic alopecia becomes a medical problem only when the hair loss is subjectively seen as excessive, premature, and distressing. The prerequisites for premature androgenetic alopecia are a genetic predisposition and sufficient circulating androgens.

Methods
This article is based largely on my experience in the management of hair loss. Original articles and expert reviews from major journals cited in Medline between 1966 and 1997 have been supplemented by information and articles cited in recently published textbooks. The following keywords were used for the Medline search: androgenetic alopecia, androgenic alopecia, common baldness and balding, premature baldness and balding, hereditary balding and baldness, male pattern and female pattern alopecia, hair loss, balding and baldness. From the abstracts of the 316 articles identified, I selected 126 references for detailed examination.

Prevalence and clinical features
By the age of 30, 30% of white men have androgenetic alopecia; by the age of 50, 50% do. White men are four times more likely to than black men develop premature balding.

Androgenetic alopecia produces patterned hair loss, beginning with bitemporal recession of the frontal hair line, followed by diffuse thinning over the vertex. Over time there is complete hair loss centrally on the vertex, producing a bald patch. The patch enlarges and joins the receding frontal hair line, leaving behind an island of hair on the frontal scalp. Eventually this island also disappears and only the marginal parietal and occipital hair remains. Ultimately the remaining hair thins and may also be lost.

In some men the loss over the vertex occurs more rapidly than the frontal loss; in others the entire frontal hairline marches back before a bald patch on the vertex develops. Less commonly, men bald in a Ludwig-type pattern, with preservation of their frontal hair line.

Most men are not aware of increased hair shedding and only notice that their hair is vanishing. Some men experience periods of increased and noticeable shedding.

Histopathology
Routine vertical sectioned scalp biopsies show that terminal anagen hairs, which normally penetrate through
the dermis into the subcutis, are replaced by secondary vellus hairs with residual angiofibrotic tracts called follicular streamers or stellae. There seem to be fewer follicles, but the miniaturised follicles can be identified on horizontal sections of scalp biopsies. An additional feature is an increased ratio of telogen to anagen hairs.

A mild to moderately dense perifollicular lymphohistiocytic inflammatory infiltrate is seen around the infundibulum in up to two thirds of biopsies, but this is relatively non-specific as it is also seen in one third of normal controls.

### Pathogenesis

A model for the pathogenesis of androgenetic alopecia must account for the histological features mentioned above, in particular the miniaturisation of the hair follicle and an increase in the ratio of telogen to anagen hairs; the systemic and local effects of androgens in promoting the condition; and the familial tendency.

### Increased telogen hair count

The "hair loss" in androgenetic alopecia is the result of stepwise miniaturisation of the hair follicle and change in hair cycle dynamics. The three phases of the normal hair cycle are shown in figure 1. During successive passages through the hair cycle the anagen phase becomes shorter and the telogen phase elongates, and the anagen to telogen ratio reduces from 12:1 to 5:1.

The duration of anagen is the main determinant of hair length; as it decreases in successive cycles, the new anagen hair is shorter than its predecessor (fig 2). Ultimately anagen duration is so short the emerging hair does not reach the skin surface and the only testimony to the presence of a functioning follicle is a pore.

As telogen hairs are more loosely anchored to the follicle than anagen hairs, the increased telogen count explains the increased hair shedding noticed during washing and combing the hair. In addition the latency period between telogen hair shedding and anagen regrowth becomes longer, leading to a reduction in the number of hairs present on the scalp.

### Follicular miniaturisation

The follicular miniaturisation that accompanies these hair cycle changes affects the papilla, the matrix, and ultimately the hair shaft. The dermal papilla is fundamental to the maintenance of hair growth and is probably the target for androgen mediated changes in the hair cycle and miniaturisation of the follicle. With reduced follicle size, the hairs they produce become finer (mean diameter reduced from 0.08 mm to < 0.06 mm), and pigment production decreases.

Miniaturisation occurs in either early anagen or possibly catagen or telogen hairs, producing a stepwise reduction in size of the follicle with each successive cycle. The cross sectional area of individual hair shafts growing on the vertex of a balding scalp remains relatively constant throughout the late anagen phase. This explains the long time lag between the start of effective therapy and clinical response.

### Systemic effects of androgens

Paradoxically the influence of androgens on hair is site specific. Prepubertal pubic, axillary, beard, and chest vellus hair follicles react to androgens by growing into terminal hairs. The same androgens miniaturise the pigmented terminal hairs on the scalp into non-pigmented vellus hairs. There is no satisfactory explanation for these different effects.

Studies in patients with androgen insensitivity syndromes and 5α-reductase type 2 deficiency have suggested that androgenetic alopecia is induced by activation of follicular androgen receptors by dihydrotestosterone. Intrafollicular androgen overactivity may be due to local factors such as increased numbers of androgen receptors or increased local production of dihydrotestosterone, or to systemic factors such as increased circulating androgens providing increased substrate for conversion to dihydrotestosterone, or increased systemic production of dihydrotestosterone at distant sites such as the prostate gland.

5α-Reductase catalyses the enzymatic conversion of testosterone to dihydrotestosterone, which binds to the same androgen receptor as the parent compound, but fivefold more avidly. Two isoenzymes of 5α-reductase, types 1 and 2, are found in the scalp in adults. Nevertheless the amount of dihydrotestosterone produced by men in the scalp is small compared with that produced in the prostate. The relative contributions of locally and systemically produced dihydrotestosterone to the balding process has not yet been established.

The degree of baldness is not correlated with the density of hair patterns on the trunk and limbs, nor with libido. This implies that the normal level of circulating testosterone after puberty is sufficient for maximal production of dihydrotestosterone.
Local effects of androgens
Loss of scalp hair occurs gradually over many years in an orderly and reproducible pattern and depends on factors within each follicle. Hair transplantation experiments show that occipital hairs maintain their resistance to androgenic alopecia when transplanted to the vertex, and that scalp hairs from the vertex transplanted to the forehead miniaturise in synchrony with their original neighbours on the scalp. This tendency of transplanted hairs to maintain the characteristics of the donor site is the basis of hair transplantation surgery.

The geographical patterning of the hair loss is associated with quantitative differences in numbers of androgen receptor and 5α-reductase activity in balding and non-balding areas of the scalp. These events are most likely a secondary phenomenon as in vitro the follicle is able to regulate its own response to androgens by enhancing expression of 5α-reductase and androgen receptors.

Inheritance of androgenic alopecia
The genetics of androgenic alopecia is complex. In general androgenic alopecia is believed to be due to an autosomal dominant gene with variable penetrance, but a polygenic inheritance has not been excluded.

Candidate genes are those involved in androgenic alopecia by restriction fragment length polymorphisms found no genetic variation in the 5α-reductase type 1 gene or the 5α-reductase type 2 gene or their regulation.

Adverse effects of androgenic alopecia
Androgenetic alopecia is, for most men, an unwanted and stressful phenomenon that diminishes satisfaction with their body image. Only 8% of non-balding men stated that going bald would concern them, while 50% with mild hair loss and 75% with moderate to severe hair loss were concerned. They said it made them look older and less physically and sexually attractive than their non-balding peers.

Nevertheless, most men deal with their hair loss without impairing their psychosocial functioning. The most distressed balding men are those with more extensive hair loss, those who are younger, have an earlier onset, and deem their balding as progressive (often arising from observation of their father) and socially noticeable. Men who are romantically unattached are also more likely to be distressed by balding.

Men outside these groups are more likely to seek treatment when they lack a strong, positive, body image. For such men any medical and surgical treatment should be complemented by measures to enhance self-esteem.

Management of androgenic alopecia
In general, people concerned about their androgenetic alopecia have four options. They can do nothing, get a wig, use medical treatment, or undergo surgery.

Without treatment, androgenetic alopecia is progressive. Nevertheless, for the vast majority of men, doing nothing is the most appropriate option, and these people tend not to present to doctors. In addition many people seeking treatment will choose to do nothing when presented with their alternatives; supportive counselling and reassurance may help them to come to terms with their hair loss.

Bogus treatments
The episodic nature of the hair loss has lead many people to believe erroneously that a treatment or action chronologically associated with the cessation of hair shedding was causally related. This has led to the evolution of a large number of over the counter products that are promoted for hair loss. Although their ingredients are generally safe for external use, they do not promote hair growth or prevent hair loss.

Medical treatment
Currently there are two treatments approved by the Food and Drug Administration in the United States for the treatment of androgenic alopecia in men: topical minoxidil and oral finasteride. The androgen receptor antagonists used to treat women are not suitable for men because of the potential risks of gynaecomastia, feminisation, and impotence.

Topical minoxidil
The 2% minoxidil solution is available over the counter in Britain, but a prescription is required for the 5% concentration. Hypertrichosis was noted as a side effect in men treated for hypertension with oral minoxidil. This led to the development of a topical formulation that was purported to arrest progression of the hair loss and regrow hair in about 90% of men; 60% had a medium to dense regrowth of hair. The large placebo response seen in this and other trials indicated that techniques used to evaluate the hair growth were far from perfect. In my experience these figures overestimate the benefit of minoxidil and only about 15% receive medium regrowth while 50% have their hair loss delayed and 35% continue to lose hair. Dense regrowth is exceptional. Much of the regrowth is of cosmetically insignificant indeterminate hairs rather than true terminal hairs, and the primary benefit is to halt progression of the balding. On stopping treatment all these new hairs are shed (table). Oral minoxidil provides no added benefit over topical minoxidil, and in view of its potential side effects, it should not be
Hair loss and regrowth with minoxidil and finasteride. Values are percentages

<table>
<thead>
<tr>
<th>Outcome on cessation</th>
<th>Minoxidil at 12 months</th>
<th>Finasteride 12 months</th>
<th>Finasteride 24 months</th>
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</thead>
<tbody>
<tr>
<td>Progression of hair loss</td>
<td>35</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>No progression of loss</td>
<td>50</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>Regrowth</td>
<td>15</td>
<td>48</td>
<td>66</td>
</tr>
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Future developments

Second generation steroidal 5α-reductase inhibitors such as turosteride, MK-963, MK-434, episteride, and MK-386, some of which also inhibit the type 1 isoenzyme, have been developed and are undergoing further investigation, as are a variety of non-steroidal inhibitors such as zinc.13

The possibility of gene therapy for androgenetic alopecia has been advanced by the development of a topical cream containing liposomes to deliver entrapped DNA selectively to hair follicles in mice.14

Though the development of a cream that could permanently restrict androgen receptor expression within the hair follicle is many years away, research is focusing in that direction.

Conclusions

The important advances in the field of androgenetic alopecia include the development of hair culture systems to investigate the pathogenesis of androgenetic alopecia and specific antagonist drugs; the increased understanding of hair cycle dynamics with the description of the latent phase in the hair cycle; and the development of finasteride (currently only available in the United States), which promises to be an effective treatment.

All of the currently available treatments are suppressive and not curative. Supporting the patients emotionally and ensuring they understand the limitations of these treatments remains one of the most important components of the management of androgenetic alopecia.

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References

Lesson of the week
Treatment resistant epilepsy or convulsive syncope?
Amir Zaidi, Peter Clough, Bruce Scheepers, Adam Fitzpatrick

The diagnosis of epilepsy is complicated by various conditions that can mimic an epileptic seizure, and cardiovascular conditions causing syncope may account for many cases of so-called secondary seizures.1 Convulsive syncope—that is, cerebral anoxic seizure activity secondary to transient global impairment of blood flow—can be difficult to differentiate from epilepsy. The differentiation is, however, important because syncope can be treated effectively, especially when it is due to a bradycardia.2 In addition, long term anticonvulsant treatment is expensive and can cause serious morbidity.3 We present the cases of three patients thought to have treatment resistant epilepsy who were subsequently found to have a cardiac condition.

Case histories
Case 1
A 32 year old woman was referred to the epilepsy clinic in January 1995 with a four year history of recurrent blackouts. She described episodes in which she became weak and had to lie on the floor followed by loss of consciousness lasting for about 1 minute with clenching of her fist and sometimes jerking, especially of the legs, but no incontinence or tongue biting. She normally recovered quickly, although she was tired afterwards. The blackouts occurred up to four times a week. In 1991, a 72 hour electroencephalogram had given normal results, but a trace taken after sleep deprivation showed some left sided slow wave changes. She was started on phenytoin for presumed epilepsy. She subsequently tried several anticonvulsant drugs including lamotrigine, sodium valproate, clobazam, vigabatrin, carbamazepine, and gabapentin with no significant improvement apart from a short period when clobazam was introduced. Her condition had deteriorated with gabapentin.

At referral she was taking clobazam, vigabatrin, and carbamazepine. She was changed to carbamazepine only (800 mg daily) with little effect on the frequency of attacks. Repeat ambulatory electroencephalography and magnetic resonance imaging of the brain gave normal results. She was admitted to the David Lewis Centre in November 1996 for assessment. She had a typical attack during ambulatory electroencephalographic monitoring. Immediately before the attack a sinus pause of about 5 seconds was recorded on her electrocardiogram, and she was transferred to a coronary care unit for further assessment. Electrocardiographic monitoring showed frequent sinus pauses lasting up to 7 seconds. A dual chamber permanent pacemaker was implanted and her blackouts resolved completely.

Case 2
A 43 year old man was referred for a neurological opinion in 1991 with a six year history of recurrent funny turns. He developed buzzing in his right ear followed by severe dizziness but no loss of consciousness. Thorough investigations at his local hospital had produced no clear diagnosis. Electroencephalography and computed tomography of the brain showed no abnormality. In February 1992 he had an attack complicated by loss of consciousness and a convolution. Epilepsy was diagnosed, and he was started on sodium valproate, clobazam, vigabatrin, carbamazepine, and gabapentin with no significant improvement apart from a short period when clobazam was introduced. Her condition had deteriorated with gabapentin.

At referral she was taking clobazam, vigabatrin, and carbamazepine. She was changed to carbamazepine only (800 mg daily) with little effect on the frequency of attacks. Repeat ambulatory electroencephalography and magnetic resonance imaging of the brain gave normal results. She was admitted to the David Lewis Centre in November 1996 for assessment. She had a typical attack during ambulatory electroencephalographic monitoring. Immediately before the attack a sinus pause of about 5 seconds was recorded on her electrocardiogram, and she was transferred to a coronary care unit for further assessment. Electrocardiographic monitoring showed frequent sinus pauses lasting up to 7 seconds. A dual chamber permanent pacemaker was implanted and her blackouts resolved completely.

A primary cardiac problem should always be considered in patients with apparent epilepsy who respond poorly to treatment.

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