The natural history of androgenetic alopecia

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Summary

Androgenetic alopecia (AGA) is the most common cause of hair loss, affecting up to 80% of men and 50% of women in their lifetime.

Genetic predisposition to the disease is well known but the responsible genes have not been identified. Polymorphism in the androgen receptor gene has been recently detected in AGA.[1]

Although the role of androgens, and particularly dihydrotestosterone (DHT), in causing the disease has been established for a long time, the natural history of AGA is still not completely understood.

This paper reviews recent data about natural progression of the disease, as well as factors that may interfere with its course and long-term prognosis.

Keywords: hair follicles, baldness, polycystic ovary syndrome, coronary artery disease

Is androgenetic alopecia a slowly progressive disease?

Although androgenetic alopecia has always been regarded as a slowly progressive condition produced by step by step miniaturization of the hair follicles through several successive progressively shortened anagen cycles, recent evidence indicates that this is not always the case.

Evidence that androgenetic alopecia may deteriorate rapidly comes from different sources:

- A study by Birch *et al.*[2] on female androgenetic alopecia shows that women with low hair density do not have a proportional increase of smaller diameter hairs, but just a reduction of larger diameter hairs, suggesting that miniaturization may occur rapidly, within the space of a single cycle. The traditional concept of a slowly progressive miniaturization would, on the other hand, be associated with the presence of great variability in the hair diameter, with coexistence of hairs of very different diameters on the same area.
- A mathematic calculation of the time required for a gradual miniaturization shows that, taking into account the duration of anagen, telogen, and lag phases, it would take, in most cases, too long for a hair follicle to miniaturize through several cycles.[3]
- Clinical trials on finasteride show very well the natural progression of androgenetic alopecia in patients receiving placebo. Progression of the disease can be very rapid, with transition from Hamilton III to Hamilton V in a 5-year span.[4]

The observation that early/mild AGA is characterized by a normal hair density but a variability in the hair diameter suggests that early stages of AGA (Hamilton < III) are characterized by a step by step miniaturization. Severe/advanced AGA, on the other hand, is characterized by a low hair density without great hair diameter variability, suggesting that miniaturization is a rapid event.

All these data indicate that miniaturization may be either a progressive process occurring through several cycles or an acute event that occurs within one single cycle. Because the hair follicle size is determined by the size of its dermal papilla,[5] miniaturization might result from a gradual or sudden reduction in the number of dermal papilla cells as a result of apoptosis[6] or cellular displacement.[7]

The behavior of hair follicles and their response to androgens and other factors implicated in progression of

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androgenetic alopecia is not homogeneous, but each hair follicle seems to follow its own scheme, as demonstrated by the presence of normal and miniaturized hairs within the same follicular units. Factors involved in inducing a rapid or step by step miniaturization are still unknown, but may include androgen metabolism, scalp microorganisms, ultraviolet (UV) exposure, inflammation, and other factors inducing telogen.[8,9]

Is inflammation important?

Accumulating evidence indicates that inflammation is a common feature of androgenetic alopecia, occurring much more frequently in the scalp biopsies of patients with AGA than in those of controls.[10,11] Factors that may induce inflammation include seborrheic dermatitis, production of porphyrins, and UV exposure.[12] The role of scalp microflora in inducing scalp inflammation is still debated, but a positive association has recently been found between presence of *Demodex folliculorum* on the scalp and AGA.[13]

From a practical point of view, it is very important to distinguish between inflammation around the upper portion of the hair follicle and inflammation occurring within the connective tissue sheath that lay beneath the miniaturized follicle. The latter phenomenon may cause fibrosis of the connective sheath and may explain, at least in some follicles, why miniaturization can become an irreversible process. In fact, sclerosis of the connective sheath will definitely prevent possible descent of the follicle in the hypodermis and therefore transformation of a miniaturized follicle into intermediate/terminal follicle under drug stimulation.

We have recently shown a correlation between inflammation around the upper portion of the follicle and the presence of peripilar signs at scalp macrophotography (Fig. 1). Both of these features have a statistically significant correlation with early stages of AGA.[14]

Whether superficial inflammation contributes in aggravating and accelerating AGA is still discussed. In our opinion, however, this is likely as inflammatory cytokines-promoted telogen.[15]

Is AGA associated with other diseases?

Several studies have correlated AGA with an increased frequency of coronary artery disease (CAD).[16] Further studies have shown that the association of AGA with CAD is a consequence of the fact that men with AGA have a lipid profile that predispose to CAD.[17] As evidenced by a recent review,[18] this association is not definitely established although a large number of articles on this topic have been published in the medical literature. Our impression, however, is that the association AGA × CAD may be true for severe early onset AGA.[19]

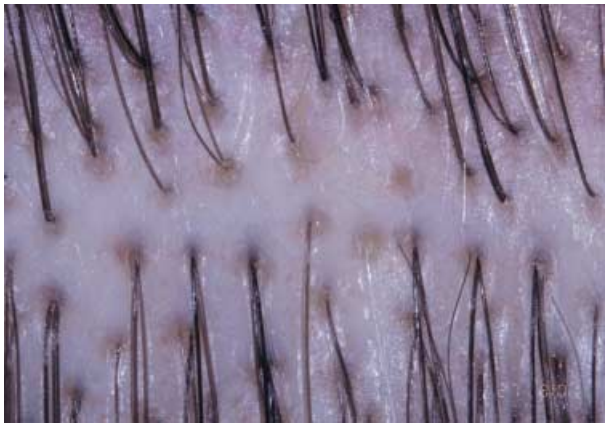

Figure 1 Evidence of peripilar signs at scalp macrophotography.

Another suggested association is that of AGA with prostate cancer. In particular, the relative risk for prostate cancer among men with baldness is 1:50. Age, genetic factors, and DHT are contributing factors for the development of both baldness and prostate cancer. Moreover, the activity of the enzyme 5α-reductase is increased in both tissues.[20]

An association has been found between early onset of AGA in men and the presence of polycystic ovary syndrome (PCOS) in their sisters.[21] In the studied family, the mode of inheritance was consistent with an autosomal dominant disorder. This has been explained by the fact that these two conditions are related, and the abnormal regulation of the enzyme P450c17α controls androgen metabolism in the ovary and the adrenal glands.

Can treatment prevent rapid progression of AGA?

Results of double-blind crossover studies with finasteride indicate that procrastinate treatment of AGA is wrong, as patients who received placebo for 1 year before starting finasteride obtained statistically lower regrowth at the end of 5 years, compared with subjects who where treated with finasteride from the beginning.[4] These data indicate that early AGA requires immediate treatment in order to give to the patients the best opportunity to regrow their hair.

Factors that may influence efficacy of finasteride in AGA are still scarce, but recent studies indicate that patients who respond to finasteride treatment have an increased expression of insulin-like growth factor (IGF-1) in the balding scalp as compared to patients who do not respond.[22]

By blocking DHT production, finasteride up-regulates IGF-1 and induces hair growth. The higher expression of IGF-1 in the dermal papilla may prolong anagen by preventing catagen. Expression of IGF-1 is, in fact, reduced during catagen phase.

Summary

The natural course of AGA may be either slowly or rapidly progressing, and reasons that influence speed of the miniaturization process are still not known. Factors that may accelerate progression include androgen metabolism, inflammatory scalp disorders, such as seborrheic dermatitis, and lifestyle. Scalp inflammation may significantly contribute to disease progression through release of telogen-promoting cytokines.

Although AGA is regarded more as a physiological condition than a disease, there is a significant association between AGA and life-threatening conditions, such as coronary artery disease and prostate cancer.

Treatments for AGA are now available although their efficacy is not absolute, and factors that distinguish responders from nonresponders are mostly unrecognized.

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