Section A -Research paper

Androgenetic Alopecia: Classification, Pathophysiology and Genetics

[1] Abdallah Hassan Kandil, [2] Kamal Ahmed El Kashishy, *[1] Mona Abdallah Attyia Khalil, [1] Elsayed Mohammed Galal khater

[1] Department of Dermatology, Venereology & Andrology, Faculty of Medicine, Zagazig University
[2] Department of Histopathology, Faculty of Medicine, Zagazig University

***Corresponding author:** Mona Abdallah Attyia Khalil

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Abstract:

Androgenetic alopecia (AGA), or male pattern hair loss, affects approximately 50% of the male population. AGA is an androgen-related condition in genetically predisposed individuals. There is no treatment to completely reverse AGA in advanced stages, but with medical treatment (eg, finasteride, minoxidil, or a combination of both), the progression can be arrested and partly reversed in the majority of patients who have mild to moderate AGA. Combination with hair restoration surgery leads to best results in suitable candidates. Physicians who specialize in male health issues should be familiar with this common condition and all the available approved treatment options.

Keywords: Androgenetic Alopecia, Hair loss, Scalp.

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Introduction:

Androgenetic alopecia (AGA), also known as male and female pattern hair loss, is characterized by non-scarring progressive miniaturization of the hair follicle with a pattern distribution in predisposed men and women. The etiology of AGA is multifactorial and polygenetic **(1)**.

Male AGA (MAGA) is clearly androgen-dependent condition and although the mode of inheritance is uncertain, a genetic predisposition is observed. In female AGA (FAGA) the role of androgens is still uncertain (**2).**

Blood-circulating testosterone is metabolized into a more potent form, dihydrotestosterone (DHT) which acts on the dermal papilla of the hair, inhibiting the duration of hair growth. Hair miniaturization is often accompanied with destruction of the erector muscle and sebaceous gland hyperplasia **(3).**

AGA is a genetically determined progressive hair-loss condition which represents the most common cause of hair loss in men. The incidence and severity is more common in Caucasian men than other nationalities **(4).**

AGA is the most common form of alopecia in both males and females. Male pattern hair loss (MPHL) usually starts between adolescence and the age of 30 years (an early start predicts a more severe form of MPHL) and affects up to 80% of male population. Female pattern hair loss (FPHL) has a bimodal incidence, with the two peaks at approximately 20 (premenopausal FPHL) and 55 years of age (postmenopausal FPHL) **(5)**.

AGA is characterized by progressive miniaturization of the hair follicle, the duration of the anagen phase gradually decreases, whilst the length of telogen remains constant or is prolonged reduction of hair in anagen and a relative increase in numbers of follicles in telogen. There is also a progressive miniaturization of the entire follicular apparatus, leading to gradual conversion of terminal hairs into vellus hairs with a progressive reduction in hair density **(6)**.

The role of androgen in AGA is well established. The circulating testosterone is converted by 5a-reductase enzyme into 5adihydrotestosterone (DHT), which has tenfold higher affinity to Androgen receptors (ARs) compared to testosterone. The predisposed scalp exhibits high levels of DHT with an increased expression of the ARs **(7).**

A normal hair cycle consists of 4 phases - growth (anagen), regression (catagen), rest (telogen) and shedding (exogen) phases **(Figure 1)**. The duration of each phase changes based on the location of the hair and also personal nutritional and hormonal status and age **(1)**.

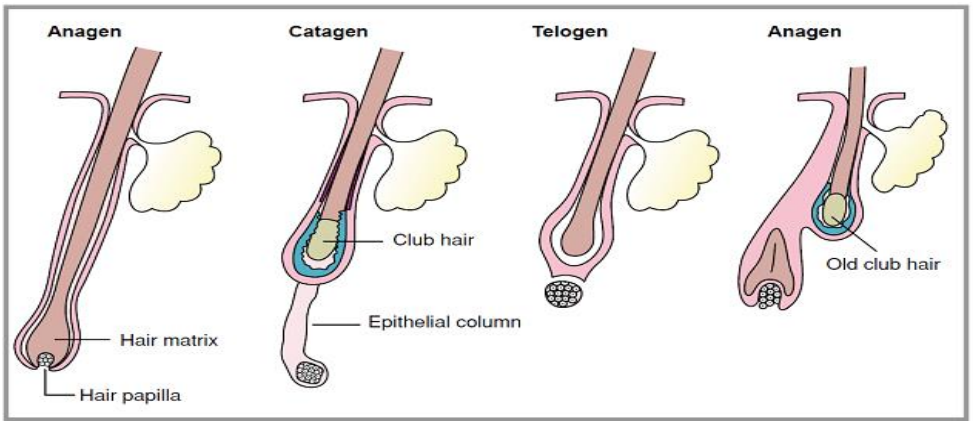

Fig. (1): Phases of Hair Cycle (1).

Classification of Alopecia

Alopecia is broadly classified into cicatricial and non- cicatricial. Cicatricial alopecia is characterised by permanent loss of hair follicles whereas non-cicatricial alopecia is reversible. AGA is the most common cause of hair loss with significant psychosocial impact on patients **(8).**

Pathophysiology

In AGA there is transformation of terminal hair to vellus hairs, associated with the activity of androgenic hormones and genetic predisposition **(Fig. 2)**. Three areas of the scalp preferentially affected are the temples, vertex scalp and midfrontal scalp **(9)**.

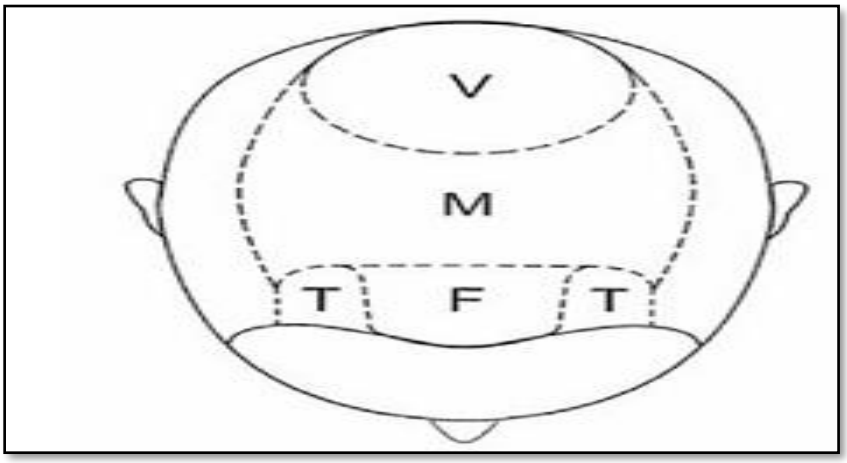

Fig. (2): Areas of scalp (F: frontal; M: mid-frontal; T:temple; V: **vertex). (9)**

As the process is patterned , bitemporal hair loss starts at the anterior hair line and moves posteriorly over the scalp. Over the vertex hair loss begins centrally and radiates outwards circumferentially whereas over the mid-frontal scalp miniaturization of hair follicle leads to a pattern of hair loss reminiscent of a Christmas tree**.** Due to reduction in the volume of dermal papilla miniaturization occurs and this is due to reduction in the number of cells and reduction in extracellular matrix **(10).**

During catagen cells travel out of dermal papilla into dermal sheath and during anagen they re-enter the dermal papilla . Miniaturisation occurs due to reduced number of cells re-entering the dermal papilla **(11).**

The cross-talk between the dermal papillae and the hair follicle cells unfolded under the influence of androgens results from the secretion of many factors from the dermal papillae which

causes premature termination of anagen and premature entry into catagen. Catagen occurs as a consequence of decreased expression of anagen maintaining factors, such as the growth factors IGF-1, bFGF and VEGF. Furthermore, an increased expression of cytokines, such as TGFb 1, IL 21a and TNF a promotes apoptosis **(12)**.

In addition sustained microscopic follicular inflammation is considered a co-factor in the etiology of AGA. A modest degree of chronic inflammation around the upper part of hair follicles has been described by many investigators . Micro inflammation may be triggered by resident microbial flora in the case of seborrhea, toxins and oxidative stress; other factors include the aging process, smoking, UV, and environmental pollutants **(6, 13).**

Role of prostaglandins (PGs) in modulating hair follicle cycle; in particular, PGs D2, E2, and F2a have the ability to regulate hair growth. Clinical data have demonstrated that PGD2 inhibits hair growth while PGE2/F2a promotes growth. Recent studies suggested that PGD2 level is elevated in male balding scalp, whereas PGE2has been shown to be reduced **(14).**

Genetics in Androgenetic Alopecia

Androgenetic alopecia is familial. Twin studies have identified 80% predisposition to baldness due to heredity. The genes influence predisposition through DNA sequence variations-single nucleotide polymorphisms, microsatellite repeats, insertion mutations, deletion mutations and copy number variations; or epigenetic modifications such as X chromosome inactivation, hypermethylation (switch off gene expression) or hypomethylation (switch on gene expression) of DNA in gene promoter regions **(7)**.

Recent genome-wide association studies in AGA have identified strong association signals in the X chromosome. Both the AR gene and the ectodysplasin A2 receptor (AR/EDA2R locus in Xq11-q12) showed strong signals for AGA **(1).**

The AR gene regulates the potency of androgen available to the hair follicle. Of the many AR gene polymorphisms known, the Stu 1 polymorphism has the most significant association with AGA. The importance of maternal lineage in the inheritance pattern of AGA is highlighted due to the location of AR on X chromosome and the strong association signal of EDA2R **(15).**

Within the follicle, mesenchyme-epithelial cell interactions are altered by androgens thereby affecting hair growth, dermal papilla size, dermal papilla cells, and keratinocyte and melanocyte activities. The Wnt signalling pathway plays a pivotal role in the action of androgen on hair growth as it regulates cells in the dermal papilla. It is hypothesised that the miniaturisation seen in AGA may be the result of a reduction in the cell number and, hence, in the size of the dermal papilla **(16).**

The arrector pili muscle serves as a source of stem cells to maintain the follicle, stimulating stem cell populations in the bulge or dermal sheath. In miniaturised follicles, there is a disruption in the function of stem cells residing in the follicle due to loss of contact between arrector pili muscle and the bulge **(17).**

FOXC1, a transcription factor which is involved in the regulation of hair development and eye. It plays an important role in the maintenance and development of hair follicle as it activates the signalling of Nfatc1 and bone morphogenetic proteins **(18)**.

Follicle integrity is maintained by arrector pili muscle by holding together each of the hair follicles in a follicular unit at the isthmus level **(19).** It is found that the arrector pili muscle degenerates and is replaced by adipose tissue in androgenetic alopecia . Adipocytes derived from the aberrant differentiation of the remaining progenitor cells in the arrector pili muscle has been speculated to cause follicle miniaturization **(12)**.

Medical treatments in FPHL and MPHL causes reactivation of growth restricted (dormant / kenogen) non vellus hair follicles. Inflammatory cell infiltrates in the follicular bulge causes progressive fibrosis of the perifollicular zone resulting in injury to follicular stem cells, which impairs the normal hair cycling with the end result of hair loss **(18)**.

The diagnosis of AGA/FPHL can be easily used in daily clinical routine since they are summarized in a clinical algorithm **(Fig. 3)**. Evidence-based guidelines on follicular and hair disorders are rare. Androgenetic Alopecia (AGA) and Female pattern hair loss (FPHL) are the most common causes of hair loss in men and women, respectively. The purpose of the presented guidelines is to help clinical doctors in their everyday practice by providing a secure diagnostic algorithm and a brief, practical checklist in order to reach a correct diagnosis with efficacy and avoid unnecessary tests **(20).**

Due to its well-known proinflammatory functions, NF-κB is considered as a potential pathogenic factor especially in epithelial cells when it is activated excessively and improperly **(Table 1)**. TNF-α, which is a proinflammatory cytokine, initiates extrinsic apoptosis pathway and increases the production of ROS markedly. It has been proposed that TGF-β is a potential anabolic factor enhancing connective tissue repair and causing the development of tissue fibrosis and demonstrated that TGF-β1 induces a rapid fibrotic response **(21)**.

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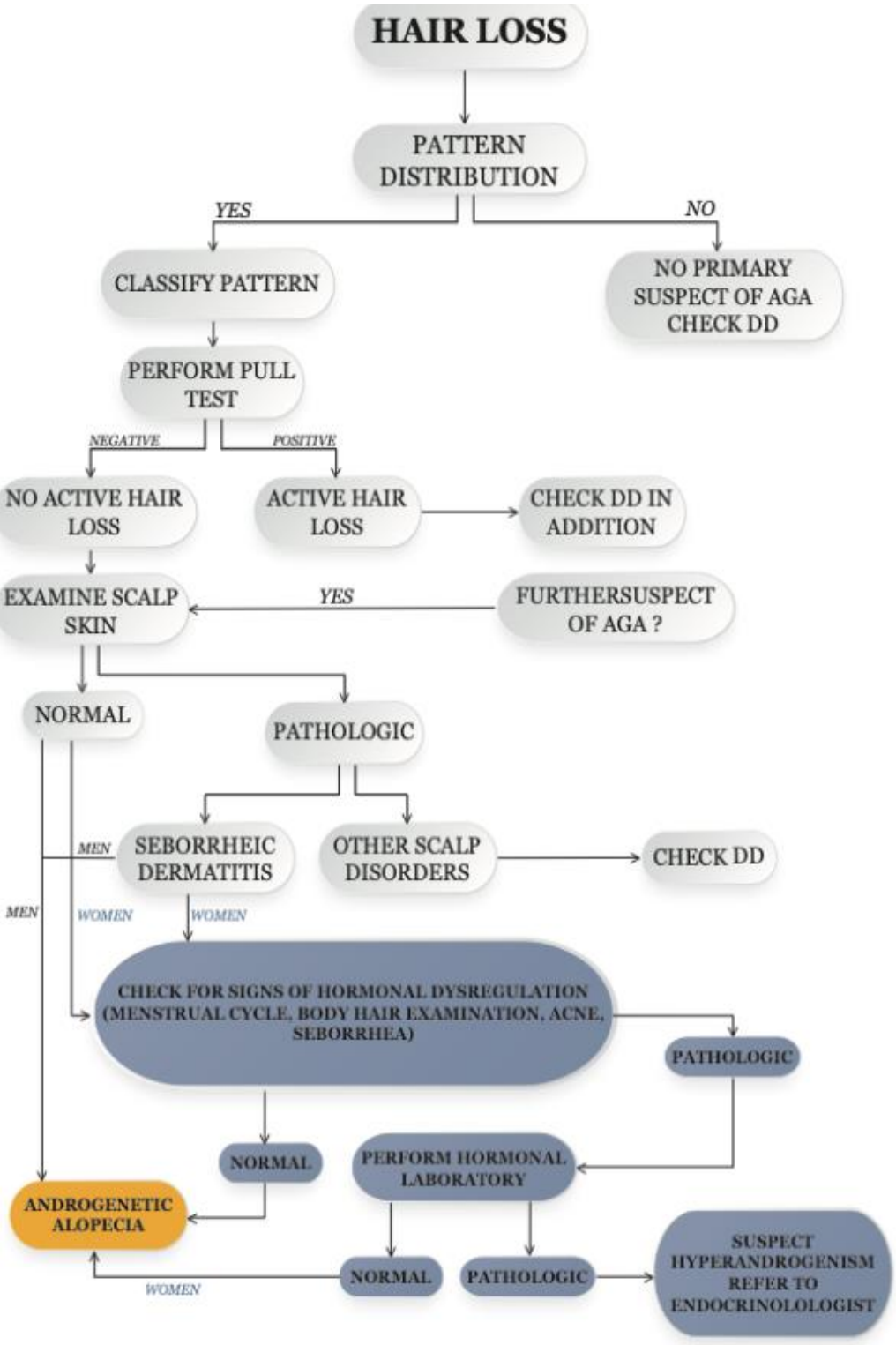

Figure 3: Algorithm for the correct diagnostic of AGA (20).

TABLE 1: Cytokines And Growth Factors Affecting Hair Development (21).

Hair morphogenesis	Activator	Catenin
	Inhibitor	Neurotropin
		BDNF
		Laminin 10
		(α5βγ1)
		FGF-7
Hair regeneration	Activator of anagen	FGF-7
		SHH
		Whn
		HGF receptor(c-met)
		PTHrp
	Inhibitor of anagen	TGF-β1
	Activator of catagen	BDNF
		NT3 and 4
		TGF-β1
		Stress
		Dexamethasone
		Trauma
		ACTH
		17β estradiol
		PGD2
	Inhibitor of catagen	Tretinoin
		FGF 5
		IGF-1
Hair differentiation	Bmp 2	
	Notch	
	Noggin	
	Hoxc 13	
	Whn	

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