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Androgenetic alopecia updates: Pathophysiology, diagnosis and treatment

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Abstract
Androgenetic alopecia (AGA) is a hereditary disorder characterized by the presence of hair follicles that exhibit sensitivity to androgens. The manifestations and progression of androgenetic alopecia are contingent upon the relationship between endocrine variables and genetic predisposition. Androgenetic alopecia is distinguished by the gradual reduction in size of hair follicles, resulting from the influence of androgens on the epithelial cells of hair follicles that are genetically predisposed and located in androgen-sensitive regions. There are varieties of medical, surgical and light-based treatment options available to slow or reverse the progression of AGA, some of these treatments are relatively new and still to be explored.

Keywords: Androgenetic alopecia, diagnosis, patterned hair loss, pathophysiology, treatment

Introduction
AGA is a hereditary condition characterized by an exaggerated reaction to androgens, impacting around 50% of both men and females. The condition is distinguished by a gradual and continuing reduction in the growth of hair on the scalp, occurring at any point after the onset of puberty. This reduction follows a distinct pattern in both men and girls [1]. In AGA, the reduction in size of hair follicles is influenced by a decrease in the duration of the growth phase (anagen) and an increase in the proportion of hair follicles (HFs) in the resting phase (telogen), which contain tiny hairs on a hairless scalp [1]. AGA is a prevalent condition characterized by hair loss, impacting over 80% of Caucasian men and 50% of Caucasian women by the time they reach the age of 70 [2].
AGA is a non-malignant medical disorder that may have substantial psychological effects on individuals, including both hormonal and genetic components. Previous research has shown that AGA may give rise to psychological challenges, such as sadness, diminished self-esteem, distorted self-perception, and reduced frequency and enjoyment of social interactions. Patients experiencing AGA as a result of ongoing illness development may encounter a decline in their overall quality of life (QOL). Consequently, the provision of therapy and counseling has paramount significance in such cases. There is a deficiency of research on the QOL in people with AGA [3].

Pathophysiology of androgenetic alopecia
The primary pathophysiological features of AGA are changes in the formation of the hair cycle, follicular shrinkage, and inflammation. The duration of the anagen phase exhibits a gradual reduction with each successive cycle, whereas the length of the telogen phase stays consistent or is extended in individuals affected by AGA. The duration of anagen phase gets significantly reduced, resulting in inadequate hair growth that fails to attain a suitable length to emerge from the skin's surface, therefore leaving an unoccupied follicular pore [4]. The process of arrector pili muscle (APM) degeneration and subsequent replacement with adipose tissue was observed. The precise mechanism underlying this phenomenon is still unknown; however, the researchers hypothesized that the degeneration of follicular stem or progenitor cells might be associated with the APM's degeneration [4].
The APM plays a crucial function in the preservation of hair follicle integrity.

The rejuvenation of the APM in transplanted hair follicle units has shown the ability to stimulate the regeneration of the neurofollicular and neuromuscular junction in the bulge region of the follicle. This phenomenon has been observed in individual follicular unit transplants performed on patients with AGA [5]. The inflammatory processes include the generation of ROS and inflammatory mediators such as TNF-a, IL-1, and histamine. These mediators have the ability to modify the immunological environment of the follicle. While they may not cause immediate damage to the follicle, they may disrupt the normal cycle dynamics and renewal of stem cells over an extended period of time [6].

Furthermore, many evidence indicate that persistent inflammation in the scalp has the potential to contribute to the occurrence of hair loss. The miniaturization process is histologically characterized by the presence of a micro-inflammatory lymphocytic infiltrate in the peri-infundibular region. Additionally, elevated levels of prostaglandin D2 (PG-D2) have been observed in bald scalps. Experimental evidence using human hair follicles and mice has shown that PG-D2 can inhibit hair growth. However, it is important to note that this study's findings have only been confirmed in male subjects [7].

Etiology of AGA

Genetic factors

The polygenic hypothesis has been widely accepted for the inheritance of AGA, due to its great incidence and the diverse spectrum of symptoms observed [7]. The development of androgenetic alopecia is impacted by androgens, with genetic predisposition also exerting a substantial effect. The etiology of androgenetic alopecia is complex and involves hereditary factors. The AR and 5-alpha reductase genes have emerged as potential candidates in the field of androgenetic alopecia [7]. A familial tendency to MAA and racial variation in the prevalence of balding is well recognized (Ellis, Sinclair and Harrap, 2002) [67].

Twin studies have shown that around 80% of the susceptibility to baldness may be attributed to hereditary factors [8]. Pattern alopecia is a polygenic condition that involves both maternal and paternal genes, and its penetrance varies. Sons are five to six times more likely to develop androgenetic alopecia if their fathers are balding due to a hereditary tendency. In order for pattern alopecia to appear, androgen is also required. It takes longer to grow beyond adolescence. Pattern baldness fails to occur in males with androgen insensitivity syndrome or those castrated before puberty.

Pattern alopecia is mostly influenced by androgen receptor and hormone metabolism. Genetic factors that are inherited account for 81% of male pattern baldness [8]. Since all follicles employ the same receptors and circulating hormones, the reasons for the various responses observed in them must be related to inherent changes in gene expression inside follicles at different places. Cosmetic hair transplants are based on the principle that transplanted follicles retain their natural androgen response. This genetic programming most likely takes place throughout the stages of embryonic patterning.

Although the exact molecular processes underlying the development of distinct follicle types are unknown, several factors, including transmembrane and extracellular matrix molecules, growth factor families (like the BMPs) and secreted signaling factors (like Eda, sonic hedgehog, and Wnt), nuclear factors (like different homeobox genes), and other factors like Hairless and Tabby, are all thought to be involved [9].

The two triplet-repeat polymorphisms of the transactivating domain - the polyglutamine (CAG) repeat, which is positioned proximal to rs6152, and the polyglycine (GGN) repeat, which is placed distal to it-and functional differences in or around AR were the focus of early study. It is well known that AGA is androgen dependent. 1998 research by Sawaya *et al*. found that men with AGA had shorter CAG repeats than controls. This finding raised the possibility that the length of the CAG repeat in AR influences androgen-mediated gene expression in hair follicles and sebaceous glands**.** The shorter polyglycine repeat (GGN-23) showed strong correlation in different research, indicating that it was either the AGA-susceptibility allele or closer to the AGA mutation. But it didn't seem like the GGN or CAG repeat polymorphisms were in charge of the connection with AGA on their own [9].

Only 77% of non-bald males had the androgen receptor gene restriction fragment length polymorphism (RFLP), which was present in almost all young bald men (98.1%) and older bald men (92.3%). Although the existence of this polymorphism in non-bald males suggests that it is essential but not sufficient to generate the phenotypic, it does seem to be necessary for the development of MAA. Furthermore, bald males were found to have greater frequencies of numerous shorter triplets repeat haplotypes than normal controls.

It seems that a functional variation of the AR gene is linked to these RFLPs. Interestingly, the X chromosome, which is transferred from a mother to a male kid, contains the androgen receptor gene. However, similar hair loss has been observed in fathers and sons in family studies, which cannot be attributed to mutations in the AR gene alone. These findings imply that the phenotype could possibly be influenced by other autosomal genes. Numerous investigations have looked at other potential genes and chromosomal locations that may be involved in hair loss [10]. Dimorphic intragenic restriction fragment length polymorphisms in 828 families were used in genetic association studies of the five alpha reductase genes, SRD5A1 on chromosome 5 and SRD5A2 on chromosome 2, however these studies were unable to demonstrate a link between these genes and MAA. But because 5 alpha reductase enzymes are involved in the conversion of testosterone to DHT and since 5 alpha reductase inhibitors may effectively cure hair loss, it is clear how important these enzymes are to MAA.

Androgenetic alopecia has also been linked to the cytochrome p450 alpha aromatase enzyme. By catalyzing the conversion of testosterone to estrogen, aromatase reduces intra-follicular testosterone levels. The expression of aromatase varies between balding and non-balding scalps. Yip *et al*. speculate that women may be predisposed to hair loss due to the aromatase gene (CYP19A1) [11]. The goal of Hillmer *et al*. was to find novel MAA susceptibility genes. A precise mapping linkage research and genome wide scan conducted on 95 families revealed substantial evidence for an MAA susceptibility gene on chromosome 3q26 [12].

This study was unable to confirm or rule out any possible associations between MAA and chromosomes 11q22-q24, 18p11-q22, and 19p13-q13. When Hillmer *et al*. finished

their second genome-wide association investigation, they discovered a very strong correlation on chromosome 20p11. This discovery raises the possibility that the 20p11 gene is connected to an as-yet-unidentified androgen-independent mechanism [13]. A new susceptibility mutation on chromosome 7p21.1 suggests that HDAC9 is the third gene that might be causing male-pattern baldnesss [14]. AGA and single nucleotide polymorphisms (SNPs) at eight chromosomal loci are strongly correlated. The strongest effect is attributed to the X-chromosomal androgen receptor/ectodysplasin A2 receptor locus (AR/EDA2R), and the androgen receptor is a highly credible candidate gene located at this locus [14].

A recent study revealed that patients with AGA had a considerably elevated concentration of tissue DKK-1 (Dickkopf 1) levels in comparison to the control group [15]. DKK1 is hypothesized to be one of the key factors underlying AGA [15] on the basis of the following findings: administration of DKK-1 partially rescued the enlargements of HF size; a single dose of DKK-1 treatment resulted in a reduction in the width of hairs; and DHT-inducible DKK_1 expression in balding DPCs induces apoptosis in follicular keratinocytes An antagonist of the Wnt signaling pathway, DKK-1 is a secreted glycoprotein. The proto-oncoprotein Wnt, when mutated or overexpressed, has the ability to stimulate cell proliferation and transformation [16].

A study has determined that both PTGDS and PTGES are overexpressed during the initial phases of AGA. PTGDR2 levels did not differ between those of affected and unaffected individuals. Possibly, the function of prostaglandins varies from the early to late stages of AGA, resulting in distinct clinical responses to treatment with medications that target PTGDR2, PTGDS, and PTGES [17]. The heritable risk remains largely unclear despite the advancements in our knowledge of the genetics of AGA. Finding more gene candidates could provide light on the pathogenesis of AGA and enable the development of more specialized treatments [17].

Hormonal

Given the high frequency and diverse spectrum of symptoms associated with AGA, Research has shown that inheritance follows a polygenic paradigm. The role of androgen in the development of male pattern hair loss is well recognized. According to James Hamilton, an American anatomist, it was observed that castrated men did not develop male accessory organs (MAA) unless they were administered testosterone [18]. The most significant regulators of hair follicles, androgens appear to be responsible for either promoting or preventing the development of terminal hair based on the genetic makeup of certain body parts. Randall *et al*.'s theory that androgens might interact with the epithelial cells of hair follicles via the papilla itself has been reinforced by the recent revelation that cells originating from the dermal papilla, grown from alopecic scalp regions, display higher amounts of androgen receptors [18]. Particularly androgen (DHT) is widely acknowledged as the primary offender. It has recently been shown that type II 5a reductase (5a-R) plays a pathogenetic role in AGA by converting testosterone (T) to DHT [19]. Type I (5αR1) and type II (5αR2) are two 5αR isoenzymes that convert testosterone to DHT irreversibly.

While 5αR2 is mostly found in androgen-dependent tissues like the prostate and epididymis, 5αR1 is found in numerous androgen-independent organs including the liver and brain [19]. It has been shown by Inui *et al*. that DPCs from AGA and beard express more 5αR2 than DPCs from other locations. Once produced, DHT and testosterone may be eliminated by converting back to the less potent 17-ketosteroids or by using cytochrome P450 aromatase to degrade them via other enzymatic pathways that result in estrogens. Hair follicles have detectable aromatase activity, and its expression in the sebaceous glands and the outer root sheath of terminal hair follicles during the anagen phase supports a local androgen-estrogen balancing mechanism and that hair follicles serve as both sources and targets of estrogen [20].

Complete androgen insensitivity is characterized by the lack of adult body hair, indicating that all androgen-dependent follicles (ARs) are required to react. On the other hand, the need for 5αR differs depending on the follicular location.

Individuals with 5αR2 deficiency exhibit a discrepancy between their body form, which tends to become more masculine, and the development of pubic and axillary hair growth, which remains consistent with feminine patterns. This indicates that testosterone has the potential to activate the axillary and lower pubic triangle follicles particular to females, but DHT is necessary for the development of male-specific follicles such as those seen in the beard, chest, and upper pubic region. The underlying mechanism by which some follicles need testosterone while others necessitate DHT for the activation of identical cell types remains unclear. However, it is hypothesized that this disparity may be attributed to the use of distinct intracellular coactivator proteins by these cells. Due to varying gene expression inside individual follicles, this seems to be yet another contradiction of androgen action in human follicles [21]. Compared to DPCs produced from non-balding follicles, the DPCs from balding scalp hair follicles had a notably higher concentration of androgen receptors. According to a recent research, hair follicles from the occipital scalp had more DNA methylation of the AR promoter than hair follicles from the vertex AGA scalp [21].

The prevention of occipital hair shrinkage and hair loss may be achieved by reduced AR expression and enhanced AR methylation [6]. There is a suggestion that women with normal testosterone levels can be more sensitive to androgens in their peripheral blood. However, FAGA has also been documented in individuals lacking androgen receptors, suggesting that an androgen-independent mechanism may be at work [6]. The potential protective effects of estrogen on human hair growth can be inferred from various observations. For instance, the higher incidence of FAGA after menopause suggests a correlation with decreased estrogen levels. Additionally, during pregnancy, the prolongation of the anagen phase of hair growth is believed to be influenced by elevated estrogen levels. Conversely, hair loss has been observed in women undergoing breast cancer treatment with tamoxifen or aromatase inhibitors, which are known to reduce estrogen levels. Furthermore, documented cases of complete hair regrowth in transsexual individuals with AGA who receive estrogen therapy further support the potential role of estrogen in hair growth [6].

Environmental and other factors that may affect AGA

The influence of environmental variables on the development of AGA is quite limited. The initiation

of AGA has been associated with several environmental conditions, including air pollution, smoking, as well as exposure to chemicals and carcinogens. These chemicals have the potential to inhibit hair growth by interfering with the systems involved in the generation of hair proteins [22]. The act of smoking has been shown to be linked to higher levels of blood androgens. Based on this observation, we have formulated a hypothesis suggesting that smoking may be connected with an elevated risk of AGA. This hypothesis is derived from the existing evidence indicating a correlation between serum testosterone and AGA**.**

According to existing literature, there is a proposed association between alcohol usage and AGA [22]. The phenomenon of stress induces vasoconstriction in the hair follicles, hence playing a role in the process of hair thinning. Stress induces heightened amounts of testosterone, which then undergoes conversion into DHT, so disrupting the cycle of hair growth. There is evidence to suggest a correlation between AGA and both benign prostatic hyperplasia and prostate cancer [23]. DPCs from male AGA patients displayed accelerated senescence *in vitro* compared to occipital DPCs in response to environmental stress, indicating oxidative stress the most recent possibility for a role in AGA pathophysiology.

DPC morphology, migration, proliferation, senescence, and TGF signaling are all drastically altered by environmental oxygen. Bald DPCs were much more vulnerable to oxidative stress than occipital DPCs and released more negative hair development regulators, TGF-1 and 2, in response [23].

Clinical picture of androgenetic alopecia

For men, hair loss is most obvious in the vertex and frontotemporal areas. For women, the frontal hairline is usually protected, but generalized apical hair loss can be seen as a wider part of hair in front. AGA signs include a steady loss of terminal hair density and a rise in the density of short, light-colored hair [24].

Female pattern androgenetic alopecia

Pattern alopecia in females presents with three primary clinical presentations. Initially, there is a diffuse thinning of the upper biparietal and vertex regions, while the anterior hair implantation line remains intact. Additionally, there is a thinning of the upper bitemporal and vertex areas, accompanied by frontal accentuation that takes the form of a triangular or Christmas tree, with hair loss arranged in a triangular configuration in the frontal-vertical region. Third, genuine vertex balding and profound recession of the frontal-temporal hairline, which are uncommon in women but commonly observed in men [25].

Male pattern androgenetic alopecia

Men present with the recession of hairline at the temples and vertex balding, Table 1.

Table 1: Modified Norwood-Hamilton Scale [26]

Type	Clinical Definition
I	A minimal degree of hairline recession is observed along the anterior border in the frontotemporal (FT) area.
II	The triangular zones of recession along the anterior border of the hair in the FT region are characterized by a proclivity towards symmetry. The posterior extension of these areas is limited to about 2 cm prior to a line delineated on a coronal plane connecting the bilateral external auditory meatus. Alopecia, specifically alopecia areata, manifests in the region around the mid-frontal boundary of the skull**.**
III	Usually symmetrical and characterized by profound FT hair recession; hair coverage is either sparse or non-existent. The posterior extent of these regions of hair recession surpasses a point located around 2 cm anterior to a line formed in a coronal plane between the external auditory meatus on both sides**.**
III (vertex)	Primarily, hair loss occurs in the vertex. Although frontal recession may occur, it does not surpass the extent observed in type III.
IV	Compared to type III, the frontal and FT recession is more severe. Additionally, hair is absent or sparse in the vertex region. The extensive hairless patches are demarcated by a band of moderately dense hair that connects the fringe with full hair on both sides of the scalp.
V	The vertex and FT areas have more hair loss than type IV, and the line of hair between them is thinner and less dense.
VI	There is hair loss in both the FT and vertex areas at the same time, and there is no hair on the bridge that goes across the crown.
VII	Only a thin line of hair in the shape of a horseshoe runs from the side, just in front of or near the ear, to the back, along the sides, and low on the frontal area.
Variants	They make up 3% of all cases of AGA in men. In these people, the front edge of the hairline moves backwards all the way to the back, but there isn't a usual patch of hair in the middle of the forehead, and there isn't a bald spot growing on top of the head at the same time. The anterior retraction only moves backwards toward the head instead.
IIa	While the entirety of the antelope's border is situated high on the forehead, the customary mid-frontal area of hair is comprised of a limited number of sparse hairs. The denuded region does not extend beyond 2 centimeters from the frontal region.
IIIa	The region exhibiting denudation extends to the mid-coronal line.
Iva	The region of denudation transcends the mid-coronal line, and substantial hair thinning may occur posterior to the hairline itself**.**
Va	The most advanced form of alopecia is characterized by a partial baldness of the vertex.

Scoring of androgenetic alopecia

Several classifications exist for assessing AGA in males; however, the modified Norwood-Hamilton classification is the most widely accepted. Following in the footsteps of the previous Hamilton classification, it comprises four distinct variant varieties and seven broad groupings [26].

Modified Norwood Hamilton classification

- **Group I:** A minimal degree of hairline recession is observed along the anterior border in the frontotemporal (FT) area.
- **Group II:** A tendency toward symmetry characterizes the triangular areas of recession along the anterior

border of the hair in the FT region.

- **Group III**: Usually symmetrical, characterized by profound FT hair recession, sparsely covered with hair, or hairless.
- **Group IIIV:** (Vertex) primarily, hair loss occurs in the vertex. Although frontal recession may occur, it does not surpass the extent observed in type III.
- **Group IV:** Compared to type III, the frontal and FT recession is more severe. Additionally, hair is absent or sparse in the vertex region. Extensive hairless patches are delineated by a swath of moderately dense hair that connects the fringe, which consists of complete hair, on either side of the head.
- **Group V:** The area of hair loss at the vertex and FT is more pronounced compared to type IV, with a narrower and sparser band of hair separating them.
- **Group VI:** The hair loss is contiguous across the FT and vertex regions, and there is no hair bridge that traverses the crown.
- **Group VII:** The distribution of hair on the human scalp is limited to a certain region, namely a narrow horseshoe-shaped band. This band originates at a lateral position directly anterior to the ear and continues posteriorly down the sides, as well as reaching a lower extent on the occipital area.
- **IIa:** The anterior boundary of the hairline is positioned at a higher level on the forehead, with the typical mid-frontal region of hair being characterized by a limited number of sparse hairs. The extent of denudation is limited to a maximum distance of 2 centimeters from the frontal region.
- **IIIa:** The extent of denudation encompasses the region up to the mid coronal line.
- **IVa:** The denudation region beyond the mid coronal line, potentially resulting in significant hair loss beyond the hairline [26].
- **Va:** The highest level of alopecia appears, yet the bald region does not include the whole of the vertex Figure 1 [27].

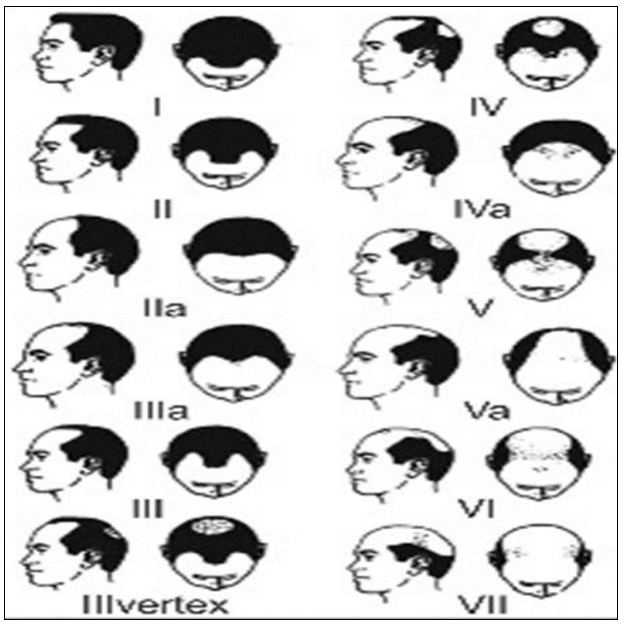


Fig 1: Modified Norwood-Hamilton classification

Ludwig's scale for female AGA

- **Grade I:** The hair on the crown exhibits noticeable thinning, which is confined to the front by a line positioned around 1-3 cm beyond the frontal hairline.
- **Grade II:** The condition of hair thinning on the crown region, namely in Grade I, is characterized by a noticeable decrease in hair density.
- **Grade III:** Complete alopecia, characterized by the entire absence of hair within the regions normally observed in Grades I and II Figure 2 [28].

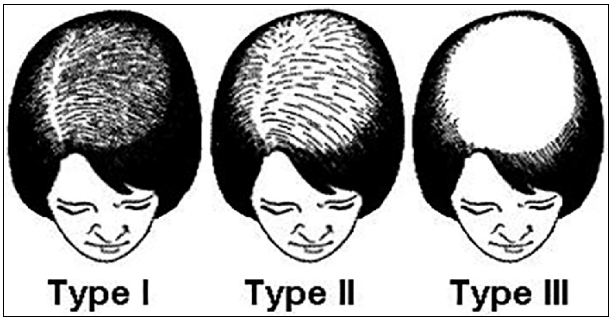


Fig 2: Ludwig's scale for female AGA

Diagnosis of androgenetic alopecia

History

Telogen effluvium (TE) is one potential reason of hair loss, but it can't be ruled out without a full medical history. History often reveals persistent hair thinning in the frontal, parietal, and/or apical regions. Trichodynia and itchiness are other possible complaints from the patient [29]. When assessing a patient's medical history, dermatologists should inquire about the presence of any preexisting conditions, drugs, mental pressures, and recent procedures that may have contributed to the patient's hair loss. It is also important to obtain a thorough menstrual history. Because of the difficulties some people have identifying a family member with hair loss, a family history for female or male pattern is useful but not essential [29].

General scalp and hair examination

In AGA, the scalp is often healthy and shows no indications of irritation. However, AGA may be exacerbated by seborrheic dermatitis and sun exposure. In order to determine whether the hair loss is patterned, a clinical examination of the hair is required [30].

Hair pull test

The hair pull is a simple clinical test for keeping tabs on conditions that cause hair loss. Evidence-based standards for the hair pull test are established in this research. The new normal range for the hair pull test is a result of 2 or less hairs, therefore washing and combing the hair at any point before the test is acceptable [31]. The investigator extracted an estimated 50 to 60 hairs from the vertex of the scalp using bundles measuring 4-6 mm in diameter, the exact amount varying depending on the hair thickness. The experimenters practiced approximating the size of the hair bundles prior to beginning testing.

The procedure used here more closely mimics hair pull tests used in clinical settings; bundle size is estimated and based on experience. Slow traction was used to draw the bundle firmly as the fingers moved down the hair shaft, holding it between the thumb, index finger, and long finger at the root. There was enough strain to cause the scalp to somewhat stretch, which resulted in some discomfort but no pain. If

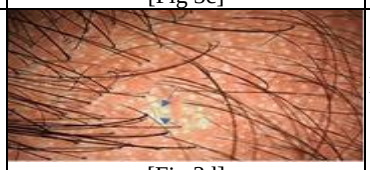
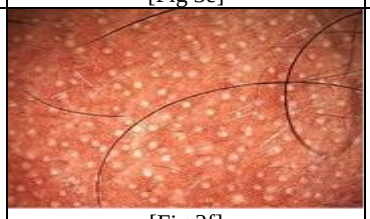
hairs were extracted, the researcher counted and recorded the amount of hairs removed [31].

Trichoscopy

The characteristic of AGA is hair shaft thickness heterogeneity (HSTH), which is >20% in male AGA (MAGA) and >10% in female AGA (FAGA), and correlates to vellus hair transformation.

1. A brown halo around the emerging hair shaft is known as the brown peripilar sign (BPPS).
2. **White peripilar sign (WPPS):** in the follicular ostium, a greater white halo
3. Round or polycyclic yellow dots are most seen in polarized light. Mirror a bare hair follicle.
4. **Focal atrichia:** Usually the size of a pencil eraser, these are patches of complete hair loss on the scalp.
5. **Scalp honeycomb pigmentation (SHCP):** melanotic rete ridges correlate with this pigmentation [32].

Table 2: Trichoscopic patterns observed in our study and their clinical correlations tab [32]

Trichoscopic pattern	Description	Trichoscopic picture Correlate	Clinical correlation
1. HSTH	The phenomenon being referred to as the characteristic feature of AGA is the change of vellus hair.	 [Fig 3a]	The phenomenon of AGA appears across both genders and age groups.
2. BPPS	In the first phases, a discernible attribute of this condition is the presence of a brown halo around the emerging hair shaft, which exhibits a diameter of roughly 1mm.	 [Fig 3b]	The first stages of AGA in both males and females.
3. WPPS	A white halo appears around the follicular ostium.	 [Fig 3c]	Observed in cases of extreme severity.
4. Yellow dots	In AGA, the presence of yellow dots that indicate empty hair follicles distended with sebum may be seen. These dots may have a circular or polycyclic shape.	 [Fig 3d]	Evident in mild and extreme forms
5. Focal atrichia	Completely bald patches on the head, about the size of a pencil eraser.	 [Fig 3e]	Appearing in the latter phases of FAGA and MAGA
6. Scalp honeycomb pigmentation	Characterized by hyperchromic borders (the melanin of the rete ridges) and hypomelanotic centers.	 [Fig 3f]	This happens a lot in bald spots with all grades of AGA.

HSTH [Fig 3a], BPPS [Fig 3b], WPPS [Fig 3c], yellow dots [Fig 3d], focal atrichia [Fig 3e], scalp honeycomb pigmentation [Fig 3f and Table 2]. Androgenetic alopecia (AGA), male androgenetic alopecia (MAGA), and female androgenetic alopecia (FAGA) are all abbreviations for variations in hair shaft thickness (HSTH), brown peripilar sign (BPPS), and white peripilar sign (WPPS) [32].

Scalp biopsy

People with alopecia get transverse sections of scalp biopsies, which are better than vertical sections for diagnosing the condition. Horizontal parts could be useful for figuring out the number, density, and percentage of follicles. It makes it possible to observe all of the hair follicles in the biopsy core. You can look into follicular growth patterns and hair morphometry [33]. Frequent vertical sectioned scalp biopsies reveal that secondary vellus hairs with remnant angiofibrotic pathways known as follicular streamers or stellae replace terminal anagen hairs as shown in Figure 4 [33].

The reticular dermis and subcutaneous tissue are home to terminal hair and follicular stelae Fig 4. The papillary dermis has stelae and vellus hairs. In short, stelae are the remaining fibrous tracts that indicate the catagen, telogen, or shrinking hair shaft and bulb movement upward [33].

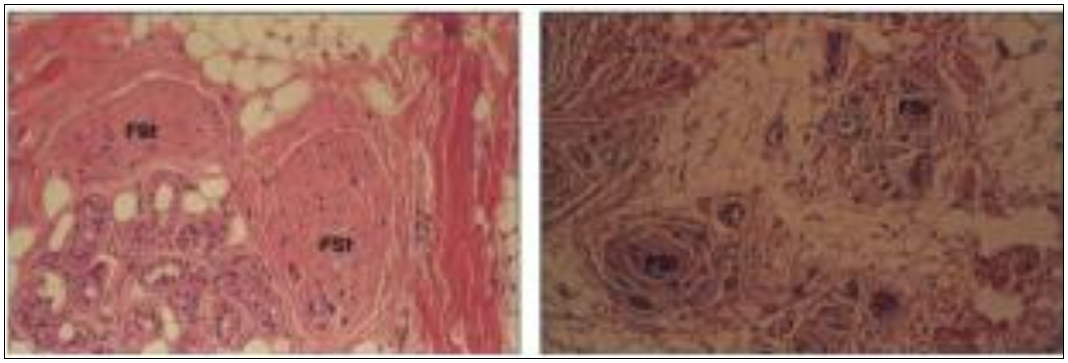


Fig 4: a and b: Stelae or fibrous streamers (FSt) commonly seen in AGA [33]

The horizontal slices of scalp biopsies reveal the presence of terminal, vellus, and vellus-like hairs inside the papillary dermis. In both male and female AGA, there was observed a decrease in the ratio of anagen-to-telogen/catagen (A: T/C), as well as an increase in the number of telogen hair follicles accompanied by a drop in the ratio of terminal-to-vellus hair (T: V) specifically in male AGA. Fibrovascular stelae have been discovered in AGA. This characteristic is seen as a consequence of hair follicle shrinkage and an augmentation in the quantity of telogen/catagen hair follicles. There is a presence of mild perifollicular fibrosis around the hair. Figure 5 [34].

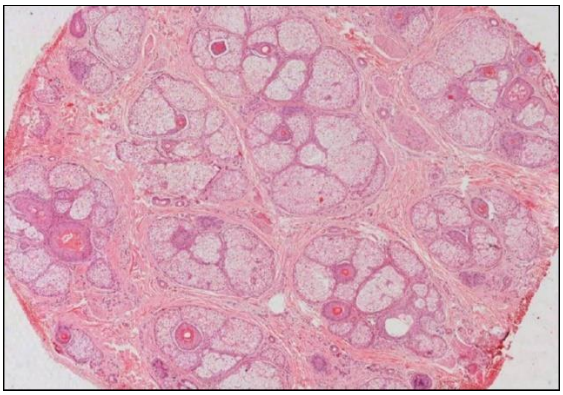


Fig 5: Miniaturized anagen, catagen, and telogen hair follicles with large sebaceous glands are observed in a biopsy of a man with androgenetic alopecia (H and E, 40) [34]

Global photography

A worldwide picture of a patient experiencing hair loss is a helpful tool for monitoring and evaluating the effectiveness of therapy. This calls for a few things, including a compliant patient with dry, clean hair and, ideally, a technician who can take the time to meticulously comb and prep the hair before every appointment. It is advisable to counsel the patient to keep their hair colored and styled the same. Take many pictures, making sure to capture every part of the scalp.

The frontal, temporal, mid-pattern, and vertex views are the four particular perspectives that are advised. The consistency of images with regard to lighting, location, and magnification is essential to effective worldwide photography. The most effective way to accomplish standardization is via a stereotactic imaging device. Global photography is thought to be the most efficient technique for evaluating hair development because it provides a uniform assessment of all the hair on the scalp [35].

Differential diagnosis

Telogen effluvium

The most frequent kind of hair loss from the scalp that is diffuse, nonscarring, and typically self-limiting lasts for around six months. It usually starts three months following a triggering event. Typically, less than 50% of the scalp's hair is lost with TE. There are two types: the acute form has spontaneous resolution and abrupt hair loss (100–1000 hairs/day) lasting two to three months. The chronic variety is characterized by mild hair loss at first (less than 100 hairs per day) and enormous hair loss that persists for over six months, with a disguised beginning. Regardless of the reason for hair loss, follicles often exhibit premature anagen termination. Subsequently, the follicle enters a catagen stage and changes into a resting state that resembles telogen. To determine the aetiology of telogen effluvium, pertinent medical history must be obtained, and laboratory tests must be performed to rule out autoimmune, nutritional, and endocrine diseases. Numerous possible factors have been linked to the pathophysiology of TE. However, people with AGA do not report significant hair loss, which is thought to be a hallmark of TE. The telogen hairs pass the hair pull test. Upon trichoscopic inspection, the whole scalp, but particularly the bitemporal region, exhibits density loss, thin hairs, and a variety of empty follicles linked to the presence of short, tiny hairs that have just begun to grow in the anagen phase [36].

Alopecia areata incognita (AAI)

AAI is a kind of hair loss characterized by a high proportion of telogen hairs on the scalp, significant hair loss, and extensive scalp thinning that typically occurs in a few months. Hair pull testing reveals telogen hairs, which are linked to trichodynia. A trichoscopic inspection reveals a large number of vellus, terminal, and regrowing hairs in addition to many spherical, uniformly colored yellow spots spread over the scalp. A few dystrophic and exclamation-like pointed hairs appear in some cases [37]. An increased number of vellus hair follicles, telogen follicles with follicular streamers that frequently contained lymphocytes, and telogen follicles were observed upon histological examination. Peribulbar inflammatory lymphocytes are observed in the filtrate surrounding vellus anagen hair follicles [37].

Frontal fibrosing alopecia with frontotemporal onset

The condition known as FFA was initially documented by Kossarden in 1994. It is distinguished by cicatricial alopecia of the frontotemporal zone of the scalp that resembles bands. Inflammation of the perifollicular zone may manifest

at the periphery of the pubescent region. Involvement of unkempt lesions of the extremities, axillary, pubic, facial, and eyebrow alopecia is a common complication. Histopathological analysis reveals lymphocytic infiltration in the vicinity of the isthmus and infundibulum, accompanied by fibrosis-induced follicle depletion. FFA is a subtype of lichen planopilaris (LPP) that predominantly affects the frontal region of women following menopause. Its human description is recent, as is the identification of newly described family cases [38].

Hereditary hypotrichosis simplex

Hypotrichosis simplex of the scalp (HSS) is distinguished by a gradual and nearly total baldness that develops in early adulthood. HSS is frequently brought on by dominant nonsense mutations in the CDSN gene that encodes corneodesmosin; these mutations result in the deposition of a substance resembling amyloid, which disrupts the regular cycle of the hair follicle. It is distinguished by the early miniaturization of hairs and is transmitted autosomally dominantly. It manifests in early childhood as slender, brittle hairs covering the entire scalp, while the development of body hair, beard, eyebrows, axillary hair, dentition, and nails continues unaffected. AGA is characterized by HF miniaturization, enlarged interfollicular spaces, and the absence of vacant follicles, as determined by trichoscopic analysis [39].

Psychogenic alopecia

It is conventionally distinguished by diffused thinning that is comparatively more pronounced in the central region of the scalp, while the frontal hairline remains unaffected. Trichomynia and extensive seborrhea, both of which are symptoms of psychosomatic and autoimmune disorders, are linked to this condition. These individuals, as determined by cognitive and psychological evaluations, suffer from anxiety, melancholy, or personality disorders. Given the absence of knowledge regarding AGA and the presence of diffused thinning, a diagnosis should be presumed. A trichoscopic examination reveals perifollicular microinflammation, follicles that are devoid of content, and hair reduction confined to the central region, excluding the frontal hairline. Hyperseborrhea is observable [40].

Triangular alopecia

Congenital triangular alopecia (CTA), sometimes referred to as temporal triangular alopecia, is a kind of hair loss characterized by a non-cicatricial pattern. Typically, the frontotemporal region is most impacted, although instances of temporoparietal or occipital scalp involvement are few. The disease under consideration is a non-progressive state that is distinguished by the presence of alopecia in the form of a triangular, oval, or lancet-shaped region. Congenital talipes equinovarus (CTEV) may manifest either prenatally or in the later stages of adulthood. The importance of four key clinical parameters was emphasized by a CTA classification system.

1. A triangular or spear-shaped area of hair loss on the scalp's frontotemporal region.
2. Typical hair follicles with vellus-type hairs surrounded by a normal terminal hair area.
3. The absence of shattered or exclamation mark hairs, as well as the absence of black or yellow spots with an intact follicular opening.
4. A lack of noticeable hair growth 6 months after dermoscopy confirmed the existence of vellus hairs.

Miniaturized and replaced by scant vellus hair follicles, hair follicles are a histological hallmark of alopecia. A trichoscopy examination shows typical hair follicles, terminal hairs, and vellus hairs [41].

Different treatment of androgenetic alopecia

Topical treatment

Minoxidil

As of now, minoxidil is the only cosmetic medicine that has been approved by the FDA to treat AGA. Minoxidil was first made as a pill to help people with high blood pressure. Minoxidil applied to the skin is used to treat AGA because oral minoxidil causes hypertrichosis in 24-100% of cases [42]. Studies have shown that minoxidil does more than just block phosphodiesterase. It also relaxes smooth muscles, makes blood vessels wider, speeds up cell growth, and lowers the body's defense system.

Minoxidil stops the production of prostaglandins 1 and 2 in human keratinocytes that have been grown in a lab. It stops the production of lysyl hydroxylase in human cells that have been grown in a lab. In arterial smooth muscle in humans, it works as a stimulator of potassium channels. More prostaglandin E2 (PGE2) is made when prostaglandin endoperoxide synthase is turned on, which has been shown in tests to help hair grow.-1 [42].

In the hair shaft, an enzyme known as minoxidil sulfotransferase (SULT1A1) turns minoxidil to minoxidil sulfate. Minoxidil sulphate opens potassium channels in cell membranes that are responsive to adenosine triphosphate. Blood tubes get bigger because of this. This makes it possible for the cell to get more air, blood, and food. Minoxidil makes the dermal papillae make more VEGF mRNA, which helps hair grow [42]. Minoxidil generally helps hair grow by reducing the telogen (resting) phase of hair cells and starting the anagen (growth) phase. This speeds up hair growth, makes hair fibers wider, and changes the hair cycle [42]. Most studies found that 24 weeks of treatment with minoxidil greatly improves the number of non-vellus hairs and all hairs. In the hair shaft, an enzyme known as SULT1A1 turns minoxidil to minoxidil sulfate. Minoxidil sulphate opens potassium channels in cell membranes that are responsive to adenosine triphosphate. This causes blood vessels to get bigger. This lets more oxygen, blood, and food get to the cell. The dermal papillae make more VEGF mRNA when you use minoxidil, which helps hair grow.

Based on the average change in non-vellus hair count, clinical studies show that 5% minoxidil works better than 2% minoxidil on men. Lower concentrations don't work, and treatments with 2% to 3% concentrations given twice a day don't make a change in how many hairs they can grow [43]. For men with AGA, it is suggested that they use 1 mL of 5% minoxidil liquids and half a capful of 5% minoxidil foam twice a day. People with FPHL should put on 1 mL of 2% MS twice a day and half a capful of 5% MF once a day as treatment. It has been shown that applying 5% MF once a day is just as good as applying 2% MS twice a day for FPHL, with a lot fewer side effect [43]. People who use minoxidil most often say that when they stop using it, their hair quickly goes back to how it was before they started using it, and they lose all the hairs that were dependent on it.

Other bad effects are itching, dandruff, and resistance in the area, most likely because it has propylene glycol in it. So, people who are allergic to minoxidil, a part of the mixture (like propylene glycol), or alcohol shouldn't use it. In addition, some users have reported that the minoxidil topical solution tends to rapidly evaporate from the scalp, resulting in oily, difficult-to-style hair. Women experience non-virilizing hypertrichosis, which predominantly impacts the cheekbones, forehead, shoulders, arms, and thighs, as one of its primary adverse effects. Even with continuous minoxidil treatment, this hair growth ceases to exist after one year; it returns within one to six months when treatment is discontinued. Minoxidil should not be administered to expectant or nursing women, despite the absence of any adverse effects observed in a prospective, large-scale study spanning one year [44].

Alfatradiol

Alfatradiol is a topical anti-androgen that works by inhibiting the enzyme 5-alpha reductase, hence reducing the conversion of testosterone to DHT. There are several research both in support of and in opposition to the efficacy of this lotion. A single open, randomized, comparative trial shown that female participants who received treatment with 0.025% alfatradiol lotion saw a reduction in total hair counts after 6 months. Conversely, the use of 2% minoxidil solution resulted in an increase in hair counts. In contrast, another open trial shown that the administration of alfatradiol led to a substantial rise in the ratio of frontal anagen/telogen hair following a treatment period of 7.5 months, including both male and female participants. It is recommended to use lotion with a concentration of 0.025% twice day [45].

Fluridil

Although topical anti-androgen fluridil is authorized for the treatment of AGA in the Czech and Slovak Republics, it is not FDA-approved in the United States. Although it is soluble in sebum and inhibits the AR in hair follicles, it does not undergo systemic absorption. After three months, the average anagen percentage of hairs from MAGA patients who applied 2% topical fluridil daily increased, whereas the average anagen percentage of hairs from patients who received a placebo remained unchanged. A 2% solution of fluridil had no effect on female AGA [46].

Prostaglandin analogues

In glaucoma patients, topical use of prostaglandin analogs resulted in noticeable brow and eyelash lengthening. Using them in AGA therapy follows from this. According to recent research, hair follicle shrinkage is associated with elevated PGD2 levels. Topical PGD2 administration has also been shown to suppress hair growth. PGF2 and PGE2 work together to promote hair growth and extend the anagen phase [47].

Latanoprost 0.1% is a version of PGF2 that was shown to greatly improve hair density and coloration after 24 weeks in a placebo-controlled study. Bimatoprost, which comes in a 0.03% eye fluid, is another PGF2 counterpart. It has been cleared by the FDA for hair hypotrichosis. It has been shown to make anagen stronger and last longer in mice. However, a case study of a postmenopausal woman with AGA did not show that locally applied 0.03% bimatoprost worked for 16 weeks [47].

Ketoconazole

Ketoconazole is categorized as an imidazole antifungal agent. Research studies have shown that the use of ketoconazole shampoo may effectively stimulate hair regrowth in women affected with AGA. The study demonstrated that a 2% KCZ micro emulsion had comparable hair stimulating effects to a standard 2% topical minoxidil in patients with FPHL. Research studies have shown that the use of ketoconazole shampoo in conjunction with oral finasteride is an efficacious therapeutic approach for addressing male AGA. The effectiveness of 2% ketoconazole shampoo has been shown in the treatment of female AGA accompanied by hyperandrogenism. This efficacy may be attributed mostly to the inhibitory effects of ketoconazole shampoo on C17-20 lyase [48].

Moreover, ketoconazole is recognized for its established anti-androgenic characteristics, since it has the ability to impede and disrupt the steroidogenesis process. Therefore, the administration of ketoconazole topically may potentially have a role in the inhibition of androgen receptor activation, thus potentially exerting a major influence on the management of hair loss associated with androgens [48].

Melatonin

The pineal gland is responsible for the secretion of melatonin in several animals, including humans. It regulates the processes of hair development, pigmentation, and molting. Two controlled trials have shown that the topical administration of a 0.1% melatonin solution greatly promotes the growth phase of hair (known as anagen) in both male and female individuals with AGA. Furthermore, this treatment has been found to be well-tolerated by the participants [49].

Caffeine

The experimental conditions were the administration of either testosterone in isolation or a combination of testosterone and caffeine, with the caffeine component including a concentration ranging from 0.005% to 0.0005%. Within the aforementioned cohort, caffeine exhibited a propensity to facilitate the development of human hair follicles by augmenting the elongation of hair shafts in both males and females ($p< 0.05$). Additionally, it was shown to extend the duration of the anagen phase in male hair follicles ($p< 0.05$), and stimulate the proliferation of keratinocytes in both males and females ($p< 0.05$) [50].

Three clinical studies were conducted to examine the effectiveness of topical caffeine in treating hair problems. Females with AGA who participated in a randomized, double-blind, parallel trial found that those who used a shampoo containing phyto-caffeine were more satisfied with their hair after 6 months of treatment than those who used a placebo (P 0.001 for both measures).

Using both frontal and occipital trichograms, 205 men with AGA took part in a randomized, open-label research comparing the efficacy of a topical liquid containing 0.2% caffeine to that of a solution containing 5% minoxidil. When comparing caffeine-based topical liquid to minoxidil for the treatment of AGA in males, the results were similar. Six months of therapy with a caffeinated liquid of 0.2% resulted in less itching of the scalp (P = 0.003). The group that was given 5 percent minoxidil didn't experience this (P = 0.211) [50].

Wnt/β-catenin pathway activators

The Wnt/-catenin pathway has become a possible therapeutic target, which means that topical Wnt activators could be a new way to treat the condition. Females responded well to a cream that contained methyl vanillate, a Wnt stimulator that comes from plants. SM04554, a very small chemical that has been shown to activate the Wnt pathway, is now being tested in humans.

In the first step of clinical study, this external treatment seemed to be safe, well-tolerated, and maybe even useful. The SM04554 external solution (0.15% and 0.25%) increased both the number of non-vellus hairs (main outcome measure) and the density of hairs (secondary outcome measure), as shown in phase II studies (press release) [51].

Systemic treatment for androgenetic alopecia

Finasteride

Finasteride is typically administered orally in doses of 1 mg daily for at least 3 months. However, response may be delayed, and therapy may be necessary for 6 months or more to obtain therapeutic objectives. Although effective, oral finasteride is linked with erectile dysfunction, decreased libido, ejaculation problems, and decreased ejaculate volume. These adverse effects are reversible if the medication is stopped. The majority of men react to finasteride; nonetheless, numerous instances of permanent sexual adverse effects related with finasteride treatment have lately been recorded [52].

Post finasteride syndrome

Recently introduced, the term "Post finasteride syndrome (PFS)" refers to a collection of adverse effects documented in small uncontrolled studies and post marketing reports that emerged during or after finasteride treatment ceased and continued to persist after the drug was discontinued. Femora sexual anhedonia, erectile dysfunction, diminished sperm count, gynecomastia, skin changes, cognitive impairment, fatigue, anxiety, depression, and suicidal ideation were among the symptoms [53].

Dutasteride

At a daily dose of 0.5 mg, dutasteride, an approved medication for symptomatic BPH, inhibits the 5 ALPHA reductase enzyme via both type I and type II isoenzymes. Dutasteride inhibits type I 5AR with an approximate threefold increase in potency compared to finasteride, and type II 5AR with a one hundredfold increase in potency.

It has been demonstrated that 0.5 mg/day of dutasteride reduces serum DHT levels by over 90%, whereas 5 mg/day of finasteride decreases serum DHT by 70%. Theoretically, therefore, it is anticipated that dutasteride would be more effective than finasteride in the treatment of males with AGA. Despite this, published data substantiating the same is scarce [54]. Dutasteride inhibits the binding of both types I and II 5-alpha-reductase enzymes. Its inhibitory effect on type II enzymes is three times more potent than that of finasteride, while its inhibitory effect on type I enzymes is one hundred times more potent. The FDA has not approved dutasteride for the treatment of FPHL; however, ongoing studies examining the inhibitor's efficacy are encouraging but primarily involve male patients. Dutasteride may be more effective than finasteride in women under the age of 50, as measured by hair thickness (not hair density) at the central and velar regions of the scalp, according to a study of women who had completed three years of treatment. A case report of a 46-year-old female diagnosed with FPHL demonstrated a partial response to treatment with 0.5 mg of dutasteride daily for six months, in contrast to the minimal response observed with finasteride and minoxidil. The available data on the adverse effects of the treatment in females is exceedingly scarce. Dutasteride is categorized as pregnancy category X due to its teratogenic nature; therefore, it is hypothesized to carry an equivalent risk of breast cancer as finasteride [54].

Estrogen and other anti-androgen treatment

Limited clinical evidence exists to substantiate the efficacy of oral estrogens or anti-androgens in preventing or ameliorating the progression of AGA. A case report involving a transsexual candidate who transitioned from male to female demonstrated the efficacy of systemic and topical estrogen in conjunction with minoxidil and Aldactone in partially reversing severe AGA. AGA in females, which is brought on by an imbalance of androgens or hormones, is treatable with two main categories of medications: anti-androgens and estrogen medicines. Included in these medications are the following:

Cyproterone acetate

For the treatment of oral anti-androgen (AR) and gonadotropin-releasing hormone in females, cyanocorticoidamide (Cyproterone Acetate) is a medication available in Europe but not in the United States. It decreases testosterone levels by inhibiting the release of luteinizing hormone and follicle-stimulating hormone, thereby blocking the AR directly. Additional applications encompass severe acne, hirsutism, and prostate cancer. It may be administered independently or in conjunction with ethinylestradiol.

For an annual period, a monthly dosage of 50 mg ethinylestradiol and 2 mg CPA is administered on days 1 through 14. It was discovered that this combination statistically increased the anagen percentage in AGA patients [55]. In the absence of hyperandrogenism symptoms among AGA women, topical minoxidil 2% was more effective, according to Vexiau *et al.* [56]. Conversely, CPA demonstrated greater efficacy in individuals with hyperandrogenism symptoms. By comparing spironolactone and CPA with a biopsy, Futterweit *et al.* [57] confirmed that hair loss had improved. The researchers discovered that, overall, 88% of women either saw their hair loss get better or stop, and there was no major difference in how well two medicines worked. Even more study needs to be done to find out if this medicine is more useful for people who have signs of hyperandrogenism. The amount that worked best was 100 mg/day from days 5 to 15 of the monthly cycle, along with 50 μg of ethinyl estradiol from days 5 to 25. CPA can make you feel down, hurt your liver, mess up your periods, make you gain weight, make your breasts hurt, and upset your stomach [55].

Spironolactone

Spironolactone is a diuretic that conserves potassium. It is administered off-label as an anti-androgen to treat hirsutism and AGA in females. It functions as a structural antagonist of aldosterone in the target tissue by inhibiting production and competitively obstructing the AR. A daily dosage of 50–200 mg is administered for a minimum of six months to

treat AGA in females. Spironolactone may induce electrolyte imbalance and postural hypotension [55].

Minor procedures for treatment of AGA

Micro needling

Micro needling is a minimally invasive dermatological procedure that punctures the stratum corneum of the skin using thin needles that are rolled over the epidermis. By means of the physical trauma caused by needle penetration, micro needling stimulates a cascade of wound healing processes that results in collagen production, neovascularization, and growth factor secretion in the treated areas with minimal epidermal injury. The utilization of micro needling as an adjunctive therapy to enhance drug delivery has demonstrated encouraging outcomes in the context of pigmentation disorders, including melasma, atrophic scars (AGA), and alopecia areata.

When used in isolation, activation of the Wnt/B-catenin pathway is a potential mechanism of action. Through the formation of microchannels through the uppermost layers of epidermis and the superficial dermis, this methodology augments the penetration of drugs [25]. Dissolving microneedles, solid, hollow, coated, or coated microneedles are all manufactured. Solid microneedles are predominantly utilized in dermatology; the number and extent of penetration, as well as the specific device (e.g., dermaroller or electric pen), may vary. The ideal depth for scalp administration is between 1.2 and 1.5 mm. A statistically significant difference was observed in draw test results, terminal/vellus hair ratio, and patient satisfaction when topical minoxidil was combined with micro needling (PRP) as opposed to PRP or minoxidil alone, according to Jha *et al* [58].

Another emerging method for skin delivery involves the utilization of hollow microneedles from professional tattoo machines to perform microinfusion of medications into the skin. One advantage of this technique in comparison to intralesional injection is the ability to deliver a minute quantity of drug consistently and uniformly into the epidermis at the same depth. This enhances the delivery of the drug to the intended target. Dissolving MNs are produced using the "poke and release" principle, which involves the encapsulation of the drug within microscopic needles. Upon insertion, the needles' polymers entirely decompose, releasing the drug into the epidermis. Coated microneedles are those that have a dispersion containing the substance coated on one side [58].

Mesotherapy

Mesotherapy, also known as intradermotherapy, involves administering pharmaceutically active substances via multiple intradermal injections at multiple locations, in close proximity to the afflicted areas, for extended durations of time compared to traditional routes. After administration, the medication attains a significantly prolonged effect and high local bioavailability. Furthermore, it has generated a favorable reaction among younger males who are in the initial phases of AGA. In recent times, mesotherapy has gained significant recognition as an unapproved, non-FDA method promoted for the treatment of various forms of alopecia, including AGA, notwithstanding the dearth of data concerning its effectiveness and potential adverse effects [59]. "Cocktails" of natural plant extracts, homoeopathic agents, vitamins, vasodilators, and medications that may stimulate hair growth, such as minoxidil and finasteride, are among the substances injected intradermally into the scalp.

Mesotherapy therapeutic agents consist of finasteride, dutasteride, and minoxidil, among others. Each of these contributes to hair growth. In addition, mesotherapy employs the vasodilators buflomedil, dihidroergotoxin, xantino nicotinate, peridil heparin, and mesoglycan sodium. Zinc, magnesium, copper, selenium, biotin, thiamine, pyridoxine, riboflavin, vitamin A, and ascorbic acid are all components of mesotherapy compounds. X-adene and dexpanthenol function as homeopathic agents [59].

For optimal results, mesotherapy is initially administered once per week for four weeks, then every two weeks for two months, and finally once per month for one to two months. Pointed injection, in which the medication is administered at the dermo-epidermal junction, and nappage, in which injections are administered at an angle of 30-60° and a depth of 2-4 mm, are both methods of scalp injection [60].

Mesotherapy is an intradermal injection technique utilizing a combination of medications and vitamins. In contrast to normal saline, Moftah *et al*. observed a significant amelioration in FPHL through the use of dutasteride-containing preparations (biotin 20 mg, dutasteride 0.5 mg, pyridoxin 200 mg, and D-panthenol 500 mg) in mesotherapy. Recently, as an adjuvant therapy for the treatment of a patient with (AGA), mesotherapy with a minoxidil-finasteride blend (1 ml minoxidil 0.5%, 1 ml finasteride 0.05%, 2 ml biotin 5mg/ml, and 2 ml D-panthenol 50mg/ml) demonstrated an outstanding response in hair regrowth [60].

Botulinum toxin

An improvement in AGA was observed in ten male patients with AGA who participated in a pilot study where 150 units of botulinum toxin were injected into the muscles surrounding the cranium (30 injection sites; dose divided). By calming the musculature of the cranium, botulinum toxin alleviates pressure on the perforating vasculature and increases oxygen concentration and blood flow. This enhanced blood flow may also result in the removal of accumulated DHT via cleansing, thereby diminishing the signal for hair miniaturization [61].

Platelet rich plasma

Because PRP is autologous, less intrusive, has less serious side effects, and is less expensive than hair restoration surgery, it has become a prominent therapy option for AGA. Platelets in concentrated plasma (often > 1,000,000 platelets/μL, or 2–7 times the natural concentration of whole blood) are prepared autologously to create PRP. The danger of infection and immunological rejection is reduced because of its autologous origin and less intrusive collecting method [62].

Laser assisted hair growth

Interest in using laser or light treatments as a therapy option for AGA and other kinds of alopecia has grown due to paradoxical hair growth after hair removal. Lasers with wavelengths between 650 and 900 nm are suitable for AGA therapy. Treatment plans call for 15 to 30 minute sessions administered on different days for 2-4 weeks, then a taper to one or two sessions per week for 6–12 months, with maintenance sessions occurring every two weeks and once a month after that [63].

Fractional laser

AGA may now be treated with fractional laser therapy, which is also effective against future hair loss [64]. When used in moderation, fractional lasers may promote hair growth. Hair regrowth after treatment with some fractional lasers has been linked to trauma-stimulated wound healing, although the exact processes by which this occurs have not been fully elucidated. Hair follicle stem cells generate offspring that migrate to the area of epidermal damage to stimulate re-epithelialization. During the anagen phase, skin wounds heal faster and more hair follicles regenerate after an injury [64].

Low level laser therapy

Laser treatment at a low level 630 nm to 660 nm devices, like combs or helmets, seem to speed up the anagen return of telogen hair cells and make the anagen phase last longer. Changes in the hair cycle show that hair density and thickness go up while hair loss goes down, which leads to clinical improvement of alopecia [2]. The terminal enzyme in the mitochondrial respiratory chain, cytochrome C oxidase (CCO), is most frequently identified as the principal photo acceptor or chromophore in LLLT [2].

On the subject of LLLT, biphasic dose response has been established in numerous *in vitro* and animal investigations. This response adheres to the Arndt-Schulz rule, which asserts that small concentrations stimulate, moderate doses inhibit, and large doses terminate for all substances. Furthermore, it seems that the impacts of LLLT are determined by the duration of illumination and irradiance (or power density; W/cm2) as opposed to fluence (or energy density; J/cm2). Variable irradiances with identical fluence produce distinct outcomes. Irradiance that is inadequate or illumination duration that is too brief will elicit no response.

Excessive levels of irradiance or prolonged periods of illumination will result in inhibitory effects. Stimulatory effects can only be achieved through an optimal equilibrium between power density and duration [2]. The proposed mechanism by which LLLT induces hair growth entails the direct stimulation of stem cells located in the bulge region of hair follicles. The proliferation and differentiation of these cells are induced by this stimulation via the upregulation of heat shock proteins (HSPs), which includes HSP27. Increasing evidence indicates that compound effects between variables may account for the transition to the anagen phase.

The impact of direct stimulation on the proliferation of outer root sheath keratinocytes (ORSKs) and dermal papilla cells (DPCs). DPCs secrete paracrine growth factors, which subsequently promote the proliferation of ORSKs [65].

Surgical treatment of androgenetic alopecia

Hair transplantation

Achieving a natural appearance through follicular unit hair transplantation, a surgical procedure for treating alopecia, involves dissecting follicular units of hair (which are naturally occurring bundles of hairs) under a stereomicroscope and transplanting them into the hairless area. The operation is conducted while the patient is under local anesthesia; between 800 and 1200 grafts are transplanted in a single session. The implementation of follicular unit transplantation has significantly reduced the invasiveness of the procedure while ensuring consistent, natural, and undetectable outcomes [25].

Counseling

Because of the psychological effects of AGA, it is crucial that patients receive appropriate counseling as part of their treatment [1, 4]. When it comes to medical treatment, it is critical to emphasize the necessity of lifelong treatment, and when it comes to surgical intervention, proper patient selection is crucial. The anticipated albeit gradual development in the case of medical management ought to be emphasized. It is particularly critical to provide the patient with realistic expectations prior to hair transplantation.

Conclusion

AGA is a prevalent dermatological condition that attracts significant patient attention. AGA may induce substantial psychological distress in the individual who is affected. A dermatologist must have a comprehensive understanding of the AGA diagnosis and treatment processes. Despite the scarcity of effective therapeutic options, AGA remains an area where expanding research is contributing to the understanding of its pathogenesis and developing newer therapeutic alternatives.

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