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ANDROGENETIC ALOPECIA: AN OVERVIEW

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Abstract

Androgenetic alopecia (AGA) is the most prevalent type of hair loss in both men and women. As the name indicates, the role of androgens and genetic vulnerability predisposes to pattern hair loss. AGA is characterized by gradual hair follicular miniaturization, brought on by the actions of androgens on genetically sensitive hair follicles' epithelial cells in androgen-dependent regions. AGA in women is called female pattern hair loss (FPHL), which is characterized by a decrease in hair density in the central part of the scalp while the frontal hairline is typically well preserved. While histologically identical, male, and female pattern hair loss are separate clinical entities. There are many known and unknown factors that influence the development of AGA, its exact pathogenesis is unclear precisely. This article discusses the current understanding of the etiopathogenesis of AGA, clinical features diagnostic tests available, and its treatment options such as various topical agents, systemic agents, and procedural interventions.

Key words: Androgenetic alopecia, Female pattern hair loss, Male pattern hair loss, Minoxidil, Androgen receptors

Introduction

Androgenetic alopecia (AGA) is the most prevalent progressive non-scarring hair loss affecting up to 80% and 50% in men and women, respectively, [1,2]. AGA is an androgen-induced hair disorder usually seen in genetically susceptible individuals causing end-organ sensitivity to androgens [3]. Its pathogenesis relies on the conversion of circulating androgen to dihydrotestosterone (DHT) peripherally in hair follicles via increased activity of 5α-reductase. DHT is thought to be responsible for follicular miniaturization that mediates the conversion of terminal hair to vellus hair [4]. AGA can lead to a considerable negative impact on social, psychological wellbeing and sorely impairing the quality of life of the affected person as it often leads to embarrassment, apprehension, and feelings of anger that further aggravate the condition [2].

Epidemiology

a- Incidence:

AGA is the most prevalent type of hair loss in the world [5]. The incidence of AGA is unknown, difficult to establish and varies with age and ethnicity. For instance, by the age of 70, AGA affects roughly 50-70% of Caucasian males and 40% of Caucasian women; however, the incidence is lower among Chinese, Japanese, Americans, and African [6]. AGA is most prevalent in the United States, affecting 40 million men, 30% of them by the age of 30, 50% of them by the age of 50 and 80% of them by the age of 70 [7]. In South African adults, the incidence of AGA was 14.6% in men and 3.5% in women, although it was a younger population than in other studies. Numerous studies conducted on Asian communities have revealed usually lower rates than those of White groups, with an all-age prevalence of about 20% for men and 5-6% for women [8].

b. Age:

The AGA onset usually appears between the age of 30–40 years and affects approximately 50% of men by the age of 50 years and 50% of women by the age of 60 years [2]. In all populations, predominance increase with age, however thinning might begin as early as puberty [8]. By the age of 70, less than 15% of males have little to no baldness [9].

c. Sex:

Both sexes are affected by AGA, which causes unique patterns of scalp hair loss [10]. This condition is referred to as female pattern hair loss (FPHL) in women and male pattern hair loss (MPHL) or common baldness in men [11].

The FPHL is estimated to affect 21 million women worldwide and while more common in post-menopausal women, it can have a relatively early onset. It affects 12 % of women around 30 years old and of 30-40% in the female between 60 and 69 years old [12].

Etiology (Pathogenesis)

AGA is a multifactorial disorder resulting from the interplay of multiple genes and environmental factors accompanied with other factors [13]. It is characterized by miniaturization of the hair follicle due to alteration in dynamics of the hair cycle, which causes the terminal hair follicle to transform into vellus and subsequent hair shedding [14].

I. **Genetic factors:**
II. AGA is an androgen dependent in genetically predisposed individu-
III. als, and genetic polymorphisms involved in

development and progres-
IV. sion of the condition are reported, however, cannot explain the full
V. paradigm of the development, and the mode of inheritance remains
VI. to be explained although weighted as an autosomal dominant trait

The extent to which hair follicles react to circulating androgens is altered by genetic factors. A weak predisposition may delay baldness until the 60s or 70s, while a strong predisposition causes baldness to appear in teenagers. The baldness gene exhibited autosomal recessive manner in women and autosomal dominant activity in men [9].

Androgenetic alopecia is an androgen dependent in genetically predisposed individuals. Genetic polymorphisms implicated in genesis and progression of the condition cannot explain the full pattern of the development, although the manner of inheritance remains explained as an autosomal dominant trait [15]. The tendency to develop AGA is polygenic and not Mendelian. Sons of alopecia-free fathers are generally not at high risk of experiencing hair loss themselves. Men who have a positive maternal grandfather history are at higher risk, and this is especially true for men who have a history of paternal alopecia [2].

The androgen receptor (AR) gene is located on the X-chromosome, which is transferred from the mother to the male offspring. This receptor gene's polymorphism was initially found to be related to AGA. The discovery of additional susceptibility genes on chromosomes 20p11 and 3q26 suggests the involvement of non-androgen-dependent mechanisms. AR gene genetic variability is a necessary condition for the emergence of early-onset AGA [16].

II. Hormonal factors

Numerous studies have proven that androgens play a crucial role in the miniaturization of hair follicles, as does the interaction between dermal papillae and hair follicle stem cells [14].

In hair follicle,
AR is localized in dermal papilla, and is not found in the outer root
sheath (ORS) or bulge indicating dermal papilla as a main target for
androgen in hair follicle.
26
Hair follicles in the frontal and vertex
regions are androgen□sensitive due to the elevated expression of
androgen receptors (ARs), whereas the occipital and temporal re-
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During puberty, DHT and androgen hormones both have selective functions. Testosterone is transformed to DHT by the enzyme 5α-reductase that has two isoenzymes: 5α-reductase type I, which is found in the liver and sebaceous glands and 5α-reductase type II, which is found in the scalp, beard, chest, liver and prostate gland [18,19]. Significant extensive increase in the production of DHT in frontal anagen hair follicles in balding men compared to frontal hair follicles in nonbalding men was established in several previous studies. Furthermore, elevated levels of 5α-reductase and the AR have been identified in the balding scalp. Androgens affect the transcription of regulating factors by dermal papilla cells to modulate hair follicle [20].

III. Inflammation

About 40% of AGA cases show moderate perifollicular lymphohistiocytic infiltration, sometimes accompanied with concentric layers of perifollicular deposition of collagen, and occasional eosinophils mast cells. In certain instances, the cellular inflammatory changes also surround lower follicles and occasionally affect the follicular stelae [21].

IV. Other factors

a. Environmental factors:

Environmental factors have also been found to play a role in the onset and/or aggravation of AGA [22]. Several environmental factors such as exposure

to ultraviolet rays and smoking have been implicated in the development of AGA, so these triggering factors should also be considered when taking the patient's clinical history [18].

Environmental pollution, thought to trigger of the earlier onset of AGA [23]. Research has focused on various environmental pollutants that may intervene with the endocrine functions and termed endocrine-disrupting chemicals (EDCs) that pose serious public health problems [24].

b. Thyroid abnormalities:

Hair loss can be brought on by Thyroid, and parathyroid disorders. Sometimes, diffuse hair loss is the first sign of hypothyroidism. It is well-known that thyroid hormone is crucial for the growth and maintenance of the hair follicle. Alopecia may arise in AGA as a result of complex interactions between androgens and thyroid hormones. In females, substantial hypophyseal hypothyroidism may play a role in AGA [25].

c. Vitamin D deficiency:

Serum vitamin D level is a factor considered in treating patients who have complained of hair loss. Vitamin D3 receptor is crucial in a population of keratinocyte stem cells in the bulge area of hair follicles. Abnormalities in vitamin D leads to impaired stem cell regeneration and attrition of hair follicle cycle. The risk of FPHL has been associated with reduced serum levels of vitamin D3, and it is suggested to assess serum D3 level in addition to other hormone assays to determine the patient's status [26].

Pathophysiology of AGA

Androgenetic alopecia is characterized by gradual thinning of hair results from reduction in the ratio of terminal hairs to shorter vellus hairs. This process, known as follicular miniaturization of the hair, is limited to specific regions of the scalp, namely the frontotemporal and vertex area in men and the crown region in women. These scalp areas are vulnerable to the effects of androgens. There is no loss of hair follicles in AGA, just miniaturized [18]. Follicular miniaturization is assumed to be caused by decrease in dermal papilla volume due to diminution in the number of cells per papilla as shown in Fig (1) [27].

Diffuse thinning of hair and occasionally increased hair shedding prior to the clinical appearance of baldness by a few years. This is due to the follicular miniaturization process which occurs in AGA does not concurrently affect all follicles [10].

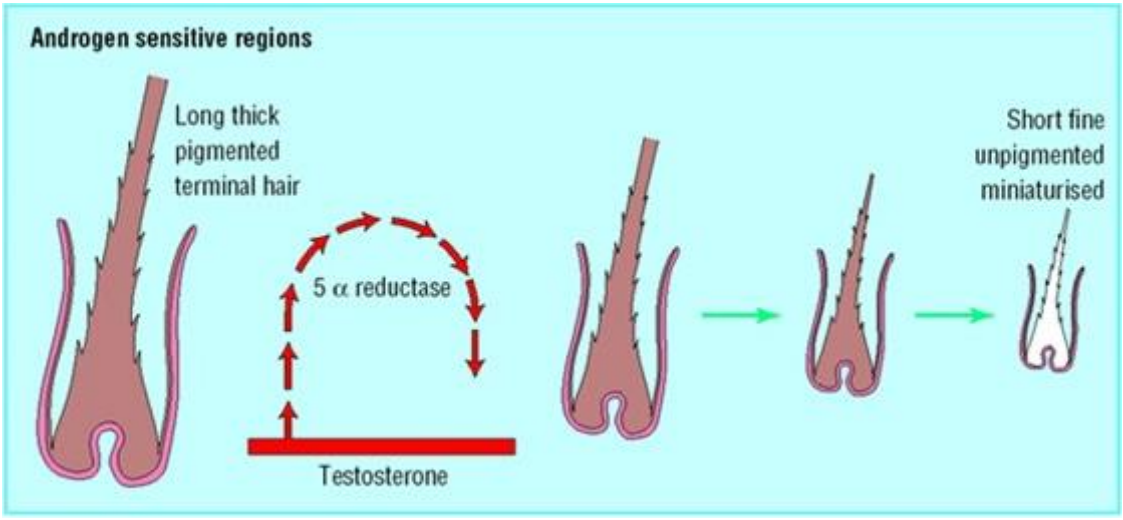

Fig (1) Progressive miniaturization of hair in each cycle [27].

Clinical picture

Male pattern hair loss:

The hair loss onset and the progression rate differ from person to person [28]. AGA mostly affects the frontotemporal area and the vertex in men, with a pattern that is consistent with the Hamilton-Norwood scale. However, in certain cases, men experience widespread crown thinning with frontal hairline retention with a pattern similar to the Ludwig type that occurs in women [29]. Hair loss begins above both temples and proceeds in a well-defined manner. The hairline gradually recedes to take on the distinctive "M" shape. Additionally, hair thins at the crown, frequently leading to partial or total baldness. MPHL is characterized by a deeper bitemporal recession that extends beyond the frontal

hair line by more than an inch. If treated early, this condition may respond to therapy [28].

Modified Norwood-Hamilton classification of male AGA (Fig 2)[14]*:*

Type I- Minimal recession of the hairline along the anterior border in the frontotemporal (FT) region.

Type II- The anterior border of the hair in the FT region has triangular areas of recession that tend to be symmetrical. These areas extend no further posterior than approximately 2 cm anterior to a line drawn in a coronal plane between the external auditory meatus on both sides. Hair is either lost or sparse along the midfrontal border of the scalp.

Type III- Characterized by deep FT hair recession, usually symmetrical and either bald or sparsely covered with hair. These areas of hair recession extend further posterior than a point that lies approximately 2 cm anterior to a line drawn in a coronal plane between the external auditory meatus on either side.

Type IIIv (vertex)- Hair is mainly lost in the vertex. There may be some frontal recession, but it does not exceed that seen in type III.

Type IV- The frontal and FT recession is more severe than type III. There is also sparseness or absence of hair in the vertex area. These bald areas are extensive but separated from each other by a band of moderately dense hair that joins the fully haired fringe on each side of the head.

Type V- The hair loss over the vertex and FT areas is larger than in type IV and the band of hair between them is narrower and sparser.

Type VI- The hair loss over the FT and vertex regions is confluent and the bridge of hair that crosses the crown is absent.

Type VII- There is only a narrow horseshoe-shaped band of hair that begins laterally just anterior to the ear and extends posteriorly on the sides and low on the occipital area.

Variants (Type variants- 'a'): Constitutes 3% of all cases of AGA: (i) the entire anterior border of the hairline progresses posteriorly without the normal island of hair in the mid-frontal region and (ii) there is no simultaneous development of a bald area on the vertex. Instead, the anterior recession just advances posterior to the vertex.

Type IIa- The entire anterior border of the hairline lies high on the forehead. The usual mid-frontal island of hair is represented by only a few sparse hairs. The area of denudation extends no farther than 2 cm from the frontal line.

Type IIIa- The area of denudation reaches the mid-coronal line.

Type IVa- The area of denudation extends beyond the mid-coronal line and there may be considerable thinning of hair posterior to the actual hair line.

Type Va- Most advanced degree of alopecia; however, the bald area does not reach the vertex.

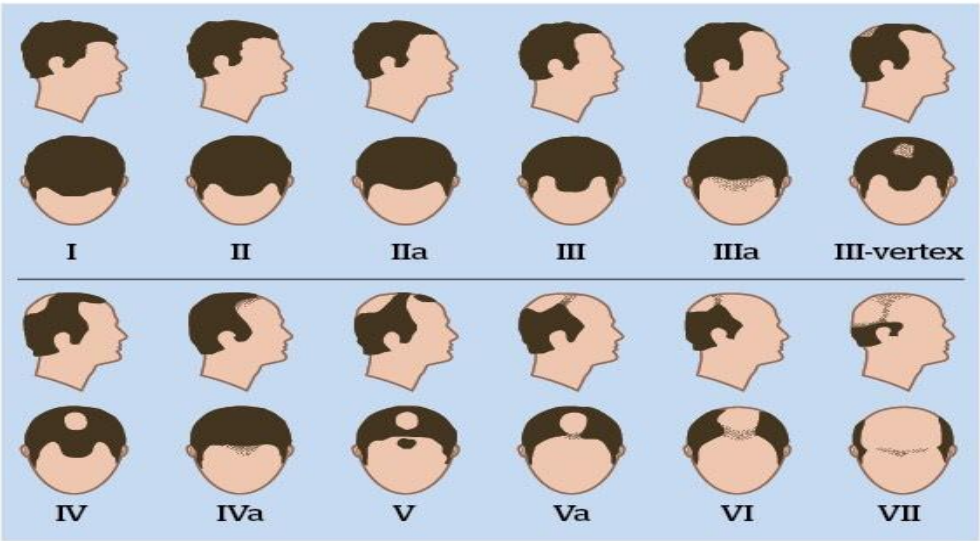

Fig (2) Modified Norwood-Hamilton classification of male androgenetic alopecia [30].

Female pattern hair loss:

In female AGA, typically has been described by diffuse thinning and widening of the central part of the scalp (crown area) with preservation of the frontal hair line. This sequence of symptoms is commonly referred to as a 'Christmas tree' pattern. Examination most frequently shows that the patient will retain her hairline (85%) and the temples area (90%). The majority will follow a Ludwig pattern; three stages of hair loss as shown in Fig (3) [31].

-Stage I: Thinning of hair is seen mainly over the anterior part of the crown with minimal widening of the parting width.

-Stage II: Thinning of the crown becomes more

evident because of an increase in the number of thin and short hairs.

-Stage III: The crown becomes almost totally bald. There is significant widening of the width, but the frontal hairline is still maintained.

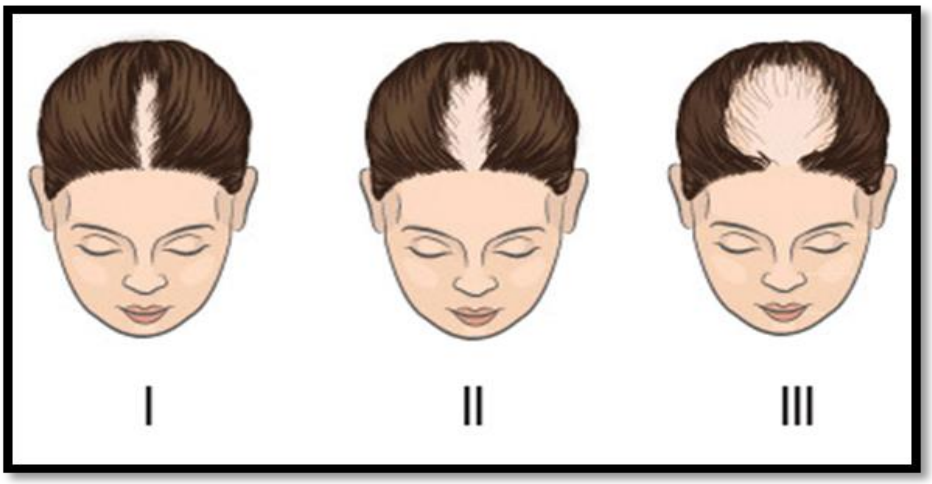

Fig (3): Ludwig scale for female hair loss: stage I, stage II, and stage III [31].

stage one of the five-point scale, represents the typical female hair pattern; stage two, denotes mild hair loss; and the remaining stages, more severe hair loss as shown in Fig (4) [10]*:*

-Stage 1: is normal. This pattern is found in all girls prior to puberty but in only forty-five percent of women aged eighty or over.

-Stage 2: shows a widening of the central part.

-Stage 3: shows a widening of the central part and loss of volume of the hair on either side of the central part.

-Stage 4: reveals the development of a bald spot anteriorly

-Stage 5: indicates advanced hair loss.

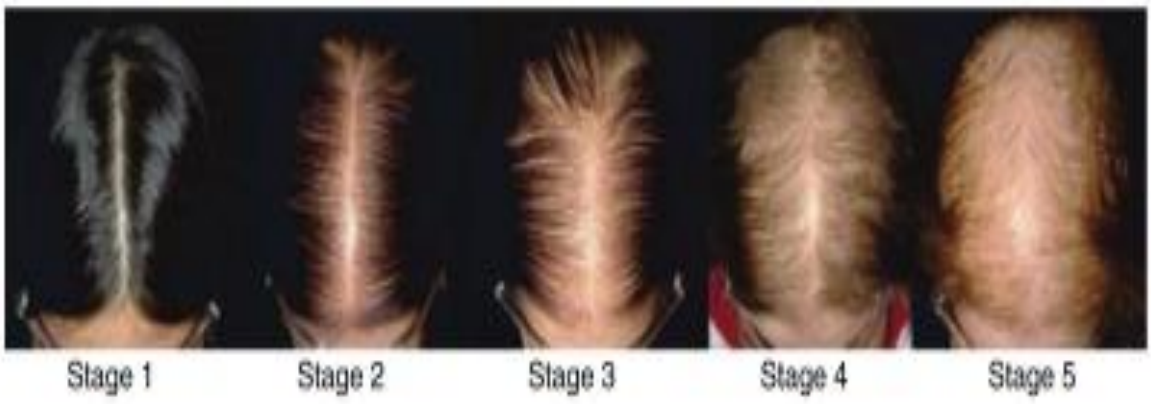

Fig (4): Sinclair scale for female pattern hair loss [10].

Diagnosis of AGA

- **History**

A complete medical history often assists in ruling out other potential causes of hair loss such as telogen effluvium. The typical history is of chronic hair loss with thinning mostly across the frontal, parietal or vertex regions. The patient might also experience itching and trichodynia. Systemic diseases history, new drugs especially within the last year should be taken. The family history of AGA is crucial because of the role of genetics in this pathology. Although a positive family history is common, a negative family history of AGA does not rule out the diagnosis [18].

Diet is another essential part of history, to rule out nutrition related effluvium. Lifestyle-related inquiries should cover the effect of traction, smoking, and ultraviolet rays' exposure on AGA, all of which have been implicated as exacerbating factors. In female patients, careful attention must be given to

evaluate any underlying hormonal dysfunction, irregular menstrual cycle, amenorrhea, difficulties in getting pregnant, miscarriages, signs of hyperandrogenism and seborrhea can all be indicators of hormonal dysfunction, such as polycystic ovary [14].

- **Clinical examination**

To assess hair density, the hair should be parted serially starting at the frontal hairline, spacing between hairs should be observed. Hair density is compared in the frontal scalp with the density of hair in the occipital scalp [32].

A full-body examination should be done to search other signs of possibly related hyperandrogenism. A full skin examination that encompasses body and nails is recommended in women sufferings from of hair loss. Nails anomalies identification is uncommon in FPHL but may distinguish the condition from other hair loss include alopecia areata, iron deficiency or lichen planus [31].

- **Laboratory investigations:**

Tests for thyroid function, a serologic test for syphilis, urine analysis, complete blood counts with differentials, and standard chemistry investigations should all be part of the laboratory workup. Free testosterone levels, and sex hormone binding globulin, dehydroepiandrosterone sulfate (DHEA-S), luteinizing hormone, follicle-stimulating hormone, androstenedione, free androgen index test and prolactin levels are also important. Hormonal assay and ovarian ultrasound are done in females to exclude polycystic ovarian disease [33].

- **Diagnostic techniques:**

A- Hair pulls test:

The pull test is an examination that is easy to perform and to repeat, to roughly judge active hair shedding. Briefly, 50–60 hairs are grasped by thumb, index, and middle fingers. While the hairs are pulled out, the fingers slide down along the hair shaft. The pull test is positive if more than 10% of the grasped hair can be pulled out. The pull test is only positive in the active phase of AGA patients due to an increase in telogen hairs in the plagued area. It may be frontally accentuated or diffusely positive [18].

B- Hair wash test:

Hair wash test has been developed to differentiate between AGA and telogen effluvium based on the count of vellus and terminal telogen hairs. The patient collects the hairs shed that are rinsed out after washing the scalp. Patients should avoid shampooing for five days prior to the test. Shed hair will be calculated in the term of total telogen hairs and the percentage of telogen vellus hairs. They are counted and separated into groups based on their length: 5 cm or longer, 3–5 cm for intermediate length, and 3 cm or shorter (referred to as telogen vellus hairs). A 10% telogen vellus hairs indicate AGA. This test is very useful in evaluating the whole scalp, but it is time consuming and double counting breaks the hair [33,34].

C- Trichogram and Phototrichogram:

The trichogram is a semi-invasive microscopic technique for assessing hair roots and hair cycle. Based on the hair cycle, the trichogram measures the quantities of hair follicles in the anagen, telogen, and catagen growth phases. Trichogram may be suggested in certain cases of FPHL if another diagnosis is suspected such as anagen effluvium or a loose anagen syndrome [14].

Phototrichogram is a non-invasive method that performs serial, close-up photographs of specific defined areas to evaluate the rate of hair growth, density of hair follicles and the thickness of hair shaft. Hair trimming is required before taking serial pictures. Other types of this technique include the contrast enhanced phototrichogram and the automated phototrichogram (Trichoscan) [35].

D- Trichoscopy:

Trichoscopy, which includes both scalp and video dermoscopy, is a non-invasive novel technique for the diagnosis of hair loss disorders such as AGA, that allows the recognition of morphologic structures not visible by the naked eye. Trichoscopy by using a video or handheld dermoscope can enhance the clinical diagnosis and follow-up for a variety of disorders affecting the hair and scalp [36].

Trichoscopy of AGA is characterized by hair shaft diameter variance of more than 20% hair shafts, the proportion of thin, vellus hairs steadily rises in AGA. Furthermore, follicles in AGA exhibit the existence of single hair unlike normal unaffected follicles that can have up to 4 terminal hairs. These features can be better clarified by doing a comparative trichoscopy of the spared occipital region. Pearly white dots, indicative of hypertrophied sebaceous glands, can be observed in long-term AGA patients. The sebaceous gland remains active even in a miniaturized terminal follicle and in fact the gland may be hypertrophied because the end organ sensitivity to circulating androgens. A unique finding that is visible in the early stages and represents perifollicular inflammation is the peripilar sign, which appears as a pale brown halo Fig (5) [35].

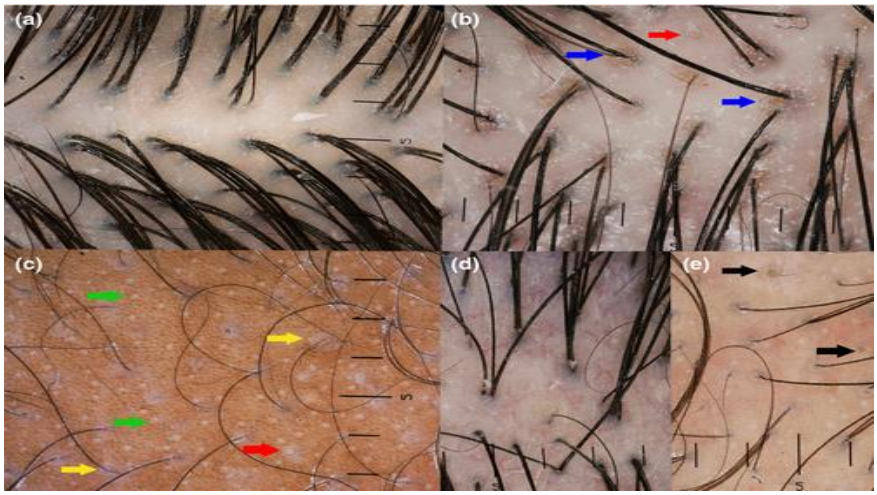

Fig (5) Trichoscopic findings in AGA. (a) Normal scalp. Hair shaft thickness heterogeneity of less than 10%. (b) AGA. Hair shaft thickness heterogeneity more than 10%, brown peripilar sign (blue arrowhead) and focal atrichia (red arrowhead). (c) AGA. Scalp honeycomb pigmentation, pinpoint white dots (green arrowhead), focal atrichia (red arrowhead) and white peripilar sign (yellow arrowhead). (d) AGA. Arborizing red lines. (e) AGA. Yellow dots (black arrowhead) (Heine Delta 20 dermatoscope, original magnification ×10) [35].

E- Genetic Testing:

The first genetic test to predict pattern hair loss risk is called HairDX. This test considers both maternal and paternal effects. Currently, genetic testing for hair loss is dependent on genotyping of the non-functional single nucleotide polymorphisms in exon 1 of AR. Even if their father shows minimal hair loss, a person with positive tests for the AR gene variant has a greater than 80% chance of developing pattern hair loss; in contrast, a person with negative tests for the AR gene variant and a father who shows no signs of hair loss has a greater than 90% chance of not developing pattern hair loss [28].

F- Scalp Biopsy:

When there is doubt about the diagnosis, 4 mm punch vertex scalp biopsies are the ideal specimens suggested. The connective tissue sheath of the lower one third of anagen follicles exhibits localized basophilic degeneration, which is the first change in AGA. Progressive miniaturization of anagen hair leads to hairs of different sizes in cross section (anisotrichosis). The vellus follicles disappear in the most advanced stages of this process, left the dermis with thin hyaline strands. Progressive fibroplasias of the perifollicular sheath are part of this process. Transverse sections of hair exhibit an increased number of telogen hairs with decreased hair diameter of individual hairs [19].

Differential Diagnosis

1) Chronic Telogen Effluvium

The most common disorder requiring distinction from FPHL is chronic telogen effluvium. This disorder is characterized by diffuse thinning of scalp hair, generally in middle-aged women, which is accompanied by widespread persistent shedding. There is no frontoparietal or central pattern of hair loss as in FPHL, but commonly there may be bitemporal recession. There is no miniaturization, and trichodynia may be reported by certain patients. The cause could be complex and challenging to establish. Typically, no trigger exists, unlike in the case of acute telogen effluvium. It can be distinguished from early FPHL using histology and trichoscopy. A hair pull is typically positive from the occiput as well as other parts of the scalp. A biopsy may be helpful in differentiating it from FPHL, as the terminal-to-vellus hair ratio in chronic telogen effluvium is often 9:1, indicating a paucity of miniaturization. An algorithm using the amount of total and ≤3-cm hairs (called telogen vellus hairs) shed per day, either alone or in combination, has been proposed as a non-invasive approach to help distinguish the two [37].

2) Diffuse and incognita alopecia areata

The autoimmune diseases known as diffuse and incognita alopecia areata are characterized by wide-spread scalp hair thinning instead of the distinctive patches seen in classical alopecia areata [38]. The diagnosis is challenging to determine when patients complain of widespread hair loss, which is described as having thinned out formerly dense hair [39]. Adult patients may experience accelerated greying of the hair due to the preferred loss of pigmented hairs. Pull tests are typically successful. Diffuse yellow spots, black dots, and dystrophic hair are visible during trichomoscopy. A biopsy is helpful in confirming the

diagnosis, which is histologically defined by Th1 cell infiltration surrounding and inside the hair follicles [38].

3) Permanent alopecia after chemotherapy

It is described as partial hair regrowth following chemotherapy, potentially brought on by the disintegration of hair follicle stem cells. The explanation is still unknown. The medications busulphan/cyclophosphamides, which are used in conditioning regimens for bone marrow transplantation, and taxanesdocetaxel and paclitaxel are the most implicated [40]. Patients have short, miniaturized hairs and moderate to severe hair thinning. Hair thinning may be more noticeable in areas of the scalp where reliant on androgen [41]. When women use aromatase inhibitors during menopause, their increased 5AR activity may cause male pattern hair loss [42].

4) Frontal Fibrosing Alopecia

Hair thinning, lack of follicular opening, and frontal hairline recession are all signs of frontal fibrosing alopecia. Unlike AGA, frontal fibrosing alopecia is a scarring alopecia and involves the loss of hair follicles [42]. It is regarded as a lichen planopilaris variant. Patients typically complain of a gradually receding frontal hairline; however, this is not necessarily the case in postmenopausal women. There may occasionally be a few sporadic terminal hairs visible in the recession band. The absence of intermediate and vellus hairs, perifollicular erythema, and scales around the surviving terminal hairs are all visible in the new hairline [43].

5) Trichorhinophalangeal syndrome

It is a very rare genetic condition. AGA-like symptoms, such as temporal area baldness and hair thinning, are present. Trichorhinophalangeal syndrome and AGA are distinguished by the absence of empty follicles and miniaturization [42].

6) Triangular alopecia

Hair loss and lesions with a triangle form start early in life and remain persistent away. AGA differs from triangular alopecia in its progression [42].

7) Myotonic dystrophy (Steinert disease)

Although there are many other signs, such as muscular weakness, wasting, myotonia, and other alterations to extra muscular tissue, there is a similar frontal hairline recession to that observed in AGA [42].

Management of AGA

The choice of treatment for AGA is contingent upon several considerations, such as efficacy, feasibility, risks, and costs. The ultimate goal is to prevent the process of miniaturization and, if possible, to reverse it. Treatments in general, people concerned about their AGA have four options. They can do nothing, get a cosmetic aids, use medical treatment, or undergo surgery [44]. All modalities of treatment must be continued to maintain the effect and the response often takes 12 or even 24 months to initially appear. Monitoring of effectiveness of treatment through clinical photography or trichoscopy is essential [45].

A. Medical treatment

I. Minoxidil

a- Topical minoxidil

The first and only topical medication that has received FDA approval for the treatment of AGA is minoxidil [6].

-Mechanism of action of minoxidil

Minoxidil is a vasodilator that was first prescribed as an oral antihypertensive medication that has been shown to induce hypertrichosis (stimulates hair growth) [46]. The specific mechanism of action is unknown. An extensive study has been performed to determine the precise mechanism by which topical use of minoxidil can promote hair growth. Minoxidil is hypothesized to increase angiogenesis and vasodilation, and to have anti-inflammatory and antiandrogenic properties [37]. The active metabolite minoxidil sulphate is thought to open the potassium channel that is sensitive to adenosine triphosphate (ATP). This increases the intracellular potential and decreases calcium entry into hair follicle cells, preventing the inhibition of hair growth caused by epidermal growth factor (EGF). Increased ATP leads to the production of adenosine, which activates the growth-promoting protein, vascular endothelial growth factor (VEGF). Moreover, cytoprotective prostaglandin synthase-1 activation, which may promote hair growth [47]. Minoxidil has been demonstrated to increase the proliferation of dermal papilla cells of the hair follicle, extending anagen and preventing cell death through antiapoptotic actions [12]. Minoxidil's effects are only sustained as long as the patient uses the medication. All hairs dependent on minoxidil will shed once the therapy is terminated, and the total density will return to a point established by natural history [48].

b- Oral minoxidil

While AGA can be effectively treated with topical minoxidil, between 30% and 60% of patients do not experience any improvement. Adherence to the topical medication can be problematic, even for patients who do not experience any side effects. Because oral minoxidil is more convenient to take than topical application, its use for FPHL seeks to both enhance adherence to treatment and increase potency. The primary drawback of oral minoxidil therapy is its potential for side effects. Because of the dose-dependent effects, using oral minoxidil at modest doses reduces side effects while maintaining a certain stimulatory impact on the hair follicle. In

recent years, oral minoxidil has been used more frequently to treat AGA in both men and women. This rapid rise can be attributed to minoxidil's ease of use, strong adherence, and perceived positive therapeutic outcomes. Larger clinical trials contrasting various doses and their results with standard topical therapy are still required, despite the drug's rapid increase in popularity [49].

II. Finasteride

Finasteride, a highly selective competitive inhibitor of type II 5α-Reductase, is approved by the U.S. FDA for AGA in men 18 years and older [50]. It binds to the enzyme permanently, blocking the conversion of testosterone to DHT. Its action is restricted to scalp hair follicles because the basic principle underlying its use is the reduction of DHT production [44].

III. Dutasteride

Both types of 5α-reductase are inhibited by dutasteride. In terms of suppressing the type I and type II 5α-reductase isoenzymes, it is around three times and more than 100 times more powerful than finasteride, respectively. Whereas finasteride only reduces serum DHT by 70%, dutasteride may reduce DHT levels by over 90. Dutasteride does not bind to the human AR [27].

IV. Antiandrogens

- **Cyproterone acetate**

Cyproterone acetate (oral anti-androgen) is a medication that inhibits gonadotropin-releasing hormone and blocks AR for treating female AGA in Europe but is unavailable in the USA. It directly blocks the AR and lowers testosterone levels by inhibiting the release of follicle-stimulating hormone and luteinizing hormone. It is used alone or with ethinylestradiol [51]. According to a recent study, topical 17-αestradiol was not as effective as finasteride 0.5% alongside minoxidil 2% in treating postmenopausal FPHL [33].

- **Spironolactone**

Spironolactone is a potassium sparing diuretic. It is used as an off-label anti-androgen medication for the management of female AGA and hirsutism. It is a structural antagonist of aldosterone that works by reducing the generation and competitively blocking the AR [33].

- **Flutamide**

Flutamide antagonizes the receptor to which testosterone and DHT bind. It is approved by the FDA to treat prostate cancer. Although it has demonstrated to be superior to finasteride and spironolactone in AGA, it is not routinely prescribed because of the possibility of hepatotoxicity, which in rare instances can result in hepatic failure. Patients with poor hepatic function should not be prescribed flutamide. Hot flashes and a diminished libido are two more minor adverse effects [38].

- **Prostaglandin analogues**

The prostaglandin analogue latanoprost promotes hair growth possibly by extending the anagen phase of the hair cycle. Elongation of eyelashes and growth of eyebrows was noticed when prostaglandin analogs were used topically for glaucoma. This leads to using them in AGA treatment [27].

V. Mesotherapy

Mesotherapy or intradermotherapy is a minimally invasive procedure that consists of intradermal infusion of a diluted mixture of active pharmaceutical agents. Once applied, the substances appear to have more potent and long-lasting effects because of increased local bioavailability, in addition to potentially lessen systemic adverse effects. The active ingredients delivered through repeated injections directly to the affected areas consists of molecules already utilized through other modes of administration, include minoxidil, finasteride, dutasteride, growth factors, panthenol, biotin, and steroids [49].

VI. Botulinum toxin

Oxidative stress, microvascular dysfunction, and perifollicular microinflammation have been reported as factors related to AGA. Furthermore, since testosterone preferentially converts into DHT in an O2-poor medium, an increased blood flow would lessen local hypoxia and may therefore be helpful in the therapy of AGA. It is well known that DHT stimulates the dermal papilla cells to produce transforming growth factor-β1 (TGF-β1), which plays a significant role in suppressing the proliferation of follicular epithelial cells. Consequently, TGF-β1 is a pro-apoptotic factor that plays a significant role in the onset of AGA and antagonizing it could constitute a way to prevent disease progression. Botulinum toxin relaxes muscles of the scalp thus lessens pressure on the perforating vasculature and promotes circulation to the bald areas. Consequently, there would be a lower rate of follicular miniaturization which is thought to be the primary pathophysiological basis of the disease as a result of ‘washout’ effect that reduces tissue DHT. Intradermal injection of botulinum toxin is a potential therapeutic avenue for AGA, as it also suppresses TGF-β1 release from hair follicles, hence adding to the previously described effects. Recent research suggests that botulinum toxin may be used to treat AGA, and this therapeutic option appears to have an adequate safety profile. Nevertheless, comprehensive research is needed to demonstrate its efficacy in both men and women [49].

VII. Laser therapy (Photobiomodulation)

Devices used for photobiomodulation therapy

often include laser diodes or light-emitting diodes, which can generate light continuously or in short, fast pulses. Patients with AGA may benefit from low-level laser therapy, which has gained popularity recently as a stand-alone or an additional treatment. In particular, 650 to 900 nm wavelengths at 5 mW may be an effective therapeutic approach for AGA patients. Paradoxical hair growth following laser or light treatments for hair removal has aroused the interest in utilizing these devices as a therapeutic option for various types of alopecia, including AGA. The precise mechanism of action of photobiomodulation in the treatment of AGA is yet uncertain. Low-level laser therapy may promote antioxidant and anti-inflammatory cytokines, as well as have a perifollicular vasodilator impact, which in turn accelerates keratinocyte and fibroblast mitosis. Evidence based studies on the effectiveness of laser therapy for AGA is currently still poor [49,52].

VIII. Platelet-Rich Plasma

Platelet-rich plasma (PRP), a novel biotechnology, is an autologous plasms preparation with concentrated platelets. PRP has the ability to increase the release of growth factors and cytokines. These factors and mediators can stimulate stem cells which assisting in hair rejuvenation [29]. PRP contains stimulatory elements called vitronectin, fibronectin, and fibrin that contribute to the development and growth of hair follicles. PRP degranulates to produce several growth factors, including insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), TGF-β1, platelet-derived growth factor (PDGF), and epidermal growth factor (EGF). Each of these growth factors play an essential role in the hair cycle, as they promotes the bulge's stem cells, responsible for the follicular unit proliferation [49].

IX. Nutritional supplements

The use of nutritional supplements in the management of AGA has also been under investigation, especially those that are hypothesized to suppress 5α-reductase, enhance the production of IGF-1, reduce oxidative stress, and provide essential nutrients or blood flow to hair follicles. Studies have indicated that 5α-reductase may be inhibited by saw palmetto, pumpkin seed oil, and the Forti 5 combo supplement. Using these supplements may help patients with AGA stabilize their hair loss or possibly encourage new hair growth. Antioxidants such as vitamin E and vitamin C have also demonstrated effectiveness in treating AGA by boosting hair density and thickness, and however side effects are limited, in large doses these effects can be paradoxical. Probiotics and protein-based supplements also seem to be therapeutically beneficial in treating AGA by supplying vital nutrients and boosting blood flow to hair follicles. Although the acceptable side effect profiles of the majority of these supplements, it is essential to note that these products might not receive FDA premarket approval, and there are currently limited studies investigating their efficacy [53]. A study has demonstrated the inhibitory effects of nutritional complex components, including linseed, borage, wheat oils, pine bark, rye grass, ß-sitosterol with omega 3-6 complex from Serenoa repens, on total 5α- reductase. Additionally, the improvement in hair quality and the decrease in greasiness show that this formulation is efficient against 5α-reductase, but it also fully exerts its attributes by restoring the physiologic state of a healthy scalp [54].

X. Gene therapy

Genes are inserted in hair follicles for therapeutic purposes for two main causes. First, single-gene mutations that impact the development of the hair shaft must be treated. The second is the treatment of polygenic hair follicle cycle anomalies that result in hair loss. Single-gene deficiency-induced defects in hair follicles must be well-phenotypically repaired, necessitating extensive and long-term gene expression in the hair follicles. Furthermore, the majority of keratinocytes in each hair follicle must express their genes usually to restore a normal hair phenotype. To accomplish these aims, it must be efficiently and reliably transduced the relevant genes into the keratinocyte stem cells. After a gene or genes have been selected to provide a therapeutic impact, they must be successfully introduced into hair follicle keratinocytes directly in vivo or ex vivo throughout tissue culture. Plasmid or viral vectors containing the desired gene are directly injected into follicular keratinocytes in an in vivo manner through methods like topical application of lipoplexed DNA or a liposome mixture containing the vectors, direct intradermal injection of the vectors, or gene gun introduction of the vectors into the hair follicle [55].

B. Hair transplant

It is a surgical hair restoration technique. Many patients may not receive the intended outcome despite having a variety of treatment alternatives; this might be due to a poor response to medication or an underlyingly advanced clinical condition. In these situations, a surgical restoration may distribute follicular units taken from another part of the patient's scalp to a specific spot, increasing the volume of hair in that area. It is important to rule out other types of alopecia that are not responsive to surgical intervention, include alopecia areata, chronic telogen effluvium, and active cicatricial alopecia. Dermatologists and plastic surgeons employ follicular units, follicular families, and follicular matching to provide both men and women healthy-

looking hair that looks natural [49].

C. Camouflage and wigs

Many patients also seek the advice of their medical professionals about options to conceal or lessen the appearance of hair loss with hair wigs, and extensions or hair camouflaging products (hair fibers, powder cakes, lotions, sprays, hair crayons, and scalp tattooing) [14].

Although scalp micropigmentation, a highly complex medical tattoo procedure for balding or thinning hair, appears incredibly simple, each patient's skin is unique when it comes to how the scalp responds to the tattoo dye, therefore each patient's experience with this innovative treatment must be customized [56].

Abbreviations

AGA, androgenetic alopecia; AR, androgen receptor; ATP, adenosine triphosphate; DHEA-S, dehydroepiandrosterone sulfate; DHT, dihydrotestosterone; EDCs, endocrine-disrupting chemicals; EGF, epidermal growth factor; FPHL, female pattern hair loss; FT, frontotemporal; IGF-1, insulin-like growth factor-1; MPHL, male pattern hair loss; PDGF, platelet-derived growth factor; PRP, Platelet-rich plasma; TGF-β1; transforming growth factor-β1; VEGF, vascular endothelial growth factor;

Author Contributions

All of the authors contributed significantly to the work, whether it was in the form of conception, designs, executions, data collection, interpretation, or any combination of these areas; they were involved in the article's drafting, revision, or critical review; they approved the final version that was going to be published; and they all agreed to take responsibility for the work in its entirety.

Disclosure

The authors declare no competing interests.

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