

An Overview about Alopecia Areata Etiopathogenesis, Diagnosis, and Management: Review Article

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ABSTRACT

Background: Rapid hair loss is caused by the chronic inflammatory disorder alopecia areata, which destroys the hair follicle. It often affects the scalp, though it can also affect other hairy areas like the beard or eyebrow. There are numerous clinical types, including patchy, alopecia totalis, alopecia universalis, and ophiasis. It may be caused by genetic, immunological, endocrine, or psychological factors.

Objective: Review of literature about Alopecia Areata etiopathogenesis, diagnosis and management

Methods: We searched Science Direct, Google Scholar as well as PubMed for relevant articles on Alopecia Areata as well as etiopathogenesis. However, only the most recent or thorough study was taken into account between October 2003 and January 2023. The authors also evaluated the value of resources culled from other works in the same genre. Documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to qualify as scientific research.

Conclusion: The primary effectors in the pathophysiology of alopecia areata condition are CD8 cytotoxic T cells. Additionally, Janus kinase (JAK) signaling pathways are upregulated. JAK inhibitors are utilized to block the signaling pathway downstream and novel therapeutic strategies that have been developed. The most prevalent place for sudden onset hair loss in alopecia areata is the scalp, and it most commonly affects adults. The absence of scales, erythema, or the exclamation marks that are pathognomonic for alopecia areata indicate that the skin is entirely healthy. Hair pull tests are often negative, with the exception of early active lesions near the periphery, which indicate disease activity and development.

Keywords: Alopecia areata, Etiopathogenesis, Management.

INTRODUCTION

Non-scarring hair loss is a characteristic of the autoimmune illness alopecia areata (AA). However, there may also be complete hair loss on the scalp or the entire body. The typical AA look is one or more coin-shaped or ovoid alopecia patches. It is the third most common kind of alopecia overall (after male and female pattern alopecia), yet it leaves no scars ⁽¹⁾.

Hair Physiology: hair growth cycle

In the hair follicle, many keratinocyte layers work together to form a hair. The length of growth cycles in the dynamic, cyclical process of hair development is controlled by a variety of hormones and cytokines and is influenced by a number of variables. Factors include

the person's age, developmental stage, food, and environmental variations like day length. Cytokines and hormones play essential roles in this cycle, instructing the follicle to alter its structure and function so that neighbouring hairs can be in different stages of the growth cycle ^(2,3,4).

The life cycle of a hair follicle consists of phases of active growth and hair shaft synthesis followed by periods of apoptosis-driven hair follicle regression and relative hair follicle quiescence. Anagen (the growing phase), Catagen (the transition phase), Telogen (the resting phase), and Exogen (the shedding phase) are the four phases of hair growth and development (shedding) ⁽⁵⁾ (Figure 1).

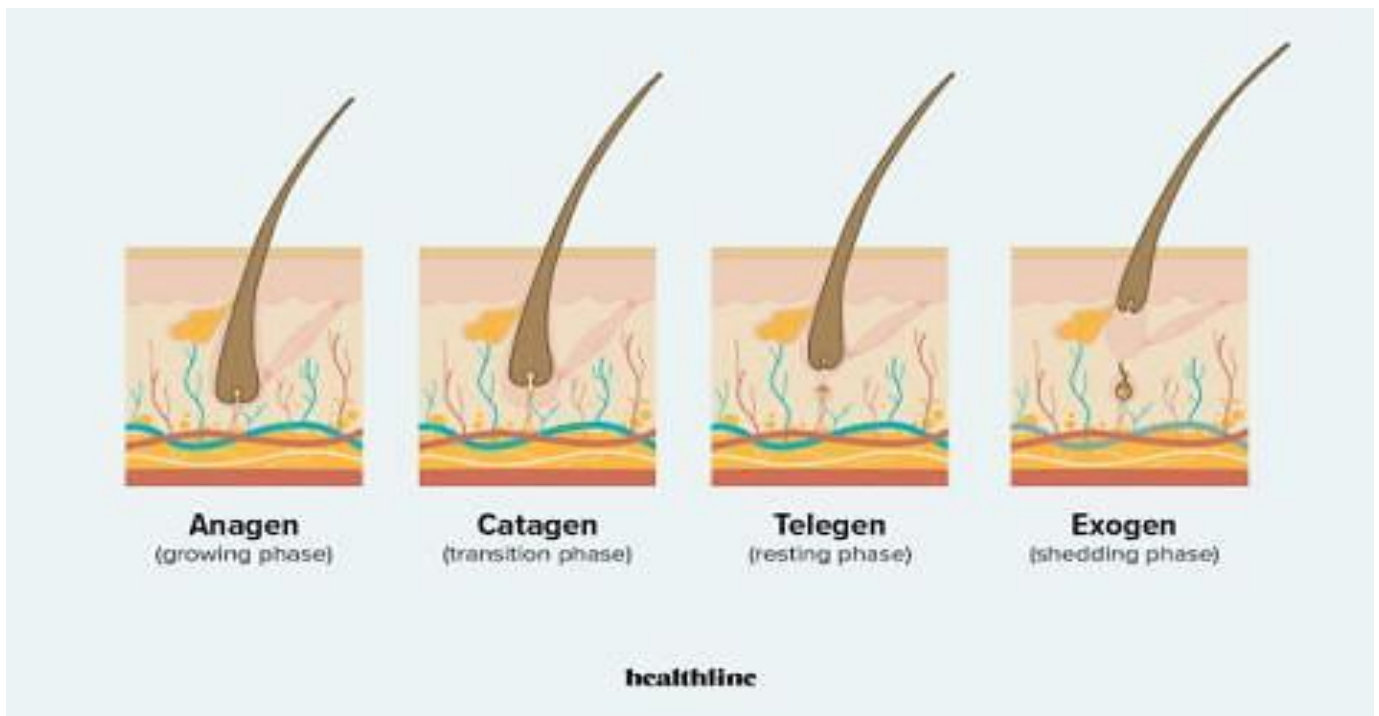


Figure (1): Hair growth cycle ⁽⁴⁾.

The formation of a hair fibre and the development of the hair follicle's distinctive onion shape occur during the anagen phase, a period of active growth. This procedure consists of six steps (I through VI) ⁽⁴⁾.

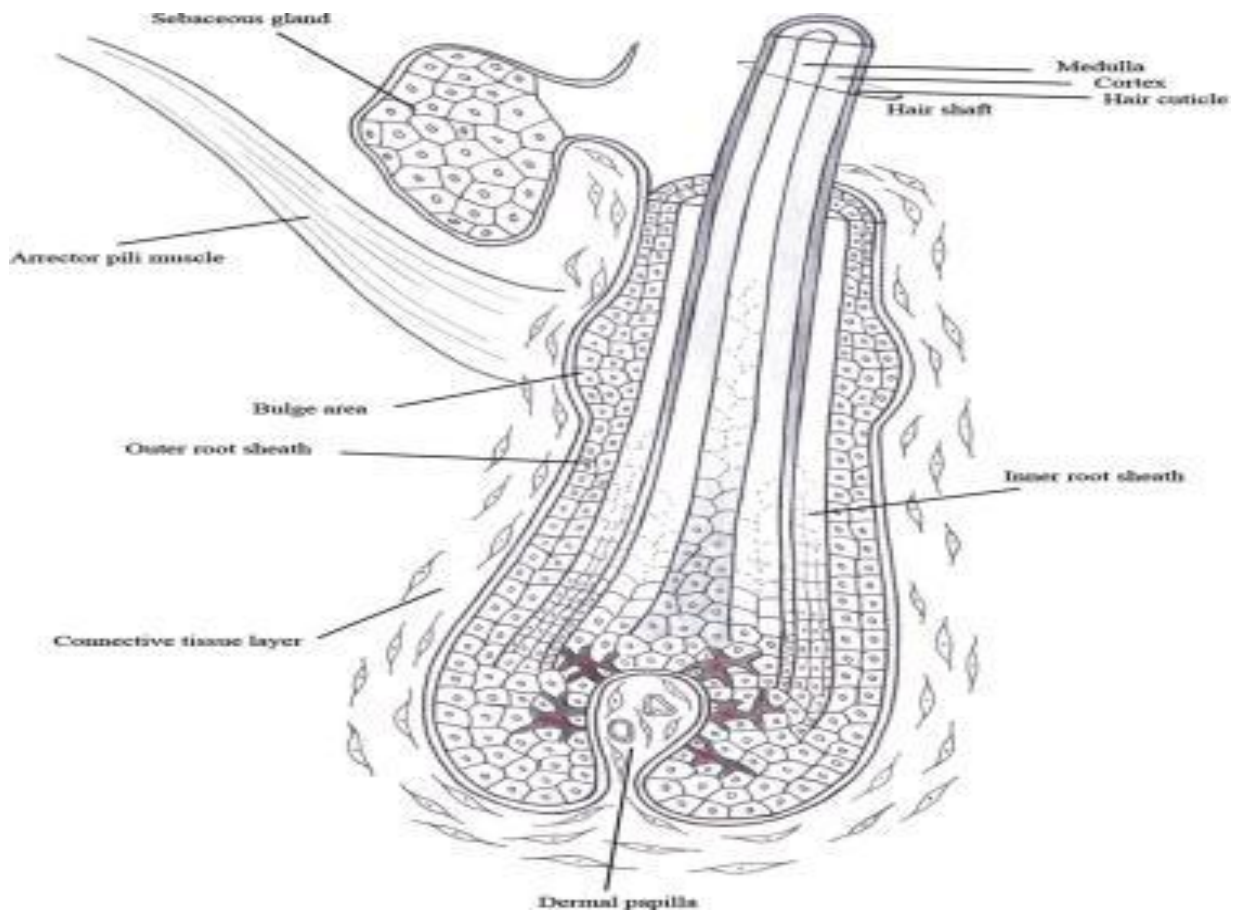


Figure (2): Anatomy and Histology of the Hair follicle ⁽⁴⁾.

In the highly mitotic anagen phase, the hair follicle generates a hair shaft; in the retrograde catagen and quiescent telogen phases, the follicle shrinks and eventually falls out. Even though only 9% of hair follicles are ever in this stage, the anagen to telogen transition can be triggered by inflammation, hormones, stress, nutritional insufficiency, lack of sleep, and drugs that inhibit cellular division. However, growth hormones, increased blood flow, and direct stimulation of the hair follicle all promote the change from telogen to anagen and subsequent hair growth ⁽⁵⁻⁶⁾.

Once the anagen growth phase has concluded, the catagen phase begins. The melanocytes' ability to produce pigment stops at the start of the catagen phase, and hair shaft development is complete. Hair matrix keratinocyte differentiation and proliferation both drastically decline. Hair follicles shrink by roughly a sixth of their original size due to apoptosis-driven regression. Catagen is responsible for the formation of the club hair, a highly specialised structure. Club hairs have an outer root sheath lined with epithelial cells that bind a keratinized brush-like structure to the telogen follicle. In order to maintain contact with the secondary hair germ and the bulge at the distal end of the hair follicle epithelium, the dermal papilla develops into a collection of quiescent cells that migrate from the subcutis to the dermis/subcutis boundary (Figure 2). There is a temporal gap of many weeks here. The telogen phase follows catagen and can continue anywhere from a few weeks (in the case of eyelashes) to eight months (in the case of body hair) (scalp hair) ⁽⁴⁾.

The dermal papilla remains in the resting phase during this stage even though the hair does not grow. Melanocytes, which produce pigment, are absent from telogen hair follicles, as is the inner root sheath. Hair follicle stem cells reside in a little cap of secondary hair germ keratinocytes that is linked closely to the dermal papilla ⁽⁵⁾. Ten to fifteen percent of all hairs are always in the resting phase. The exogen phase of this cycle results in hair loss, and the hair follicle then induces stem cells in the bulge area to restart development a few weeks later ⁽⁴⁾.

Follicular stem cells collaborate with epithelial, mesenchymal, and melanocytic cells to sustain and control the hair cycle. Hair follicle bulges may provide easy access to undifferentiated multipotent stem cells, which are crucial for hair follicle development, function, and even hair follicle colouring. Bulge activation theory suggests that papilla components communicate with bulge stem cells to modify the cycle ⁽⁷⁾.

According to this notion, signals from the dermal papilla cause the stem cells in the bulge region to start proliferating. During catagen, the follicular papilla rises, reestablishing contact with the follicular papilla bulge and starting a new hair cycle. The hair follicle's whole structure, including the hair matrix and matrix cells, originates through a process of bulk cell proliferation. The number of mitoses it can undergo is limited ⁽⁸⁾.

Hair follicles and hormones:

Insight into the potential for neuropeptides and neurotransmitters to affect stem cells and modify the hair cycle is bolstered by the close proximity of the bulge region to sensory and autonomic nerve fibres. The circumstances under which neurohormonal activities on hair follicles promote growth vary greatly. It is now understood that neuromediators aim at the non-classical mechanisms by which human hair follicles produce neurohormones. Neurohormones are produced by keratinocytes, melanocytes, and fibroblasts. Neurohormones' role in hair disorders is supported by a number of clinical studies. Acquired hypertrichosis, which is the process by which massive terminal hair follicles with a robust and pigmented hair shaft replace vellus hair follicles in humans, is known to be caused by an excessive synthesis of ACTH. The fact that ACTH causes hypertrichosis is proof that the neuropeptide may prolong or promote the anagen phase. Alopecia areata may begin as a result of extreme psycho-emotional stress, according to additional research. Another study confirmed that AA is associated with elevated levels of CRH, ACTH, and MSH. One way to accomplish this is by releasing CRH, a direct pro-inflammatory peptide. Another is by activating mast cells, which ultimately kills the hair root ⁽⁴⁾.

A typical inner root sheath is actively being created by the smaller anagen follicle as it undergoes mitosis. The cortex of a hair follicle only partially consists of keratin. These alterations suggested that hair follicle growth stops at the anagen IV stage ⁽¹⁰⁾.

Patients with total or universal alopecia had anagen follicles in the centre of their bald patches that had not yet entered the anagen III/IV phase when horizontal biopsies were performed. The cortex of the hair is just now beginning to develop beneath the conical, keratinized inner root sheath ⁽¹¹⁾.

Follicles appear to repeatedly experience shorter cycles and prematurely transition from the anagen III/IV phase to the telogen phase. The anagen phase of the hair follicles deepens when alopecia areata activity decreases ⁽⁴⁾.

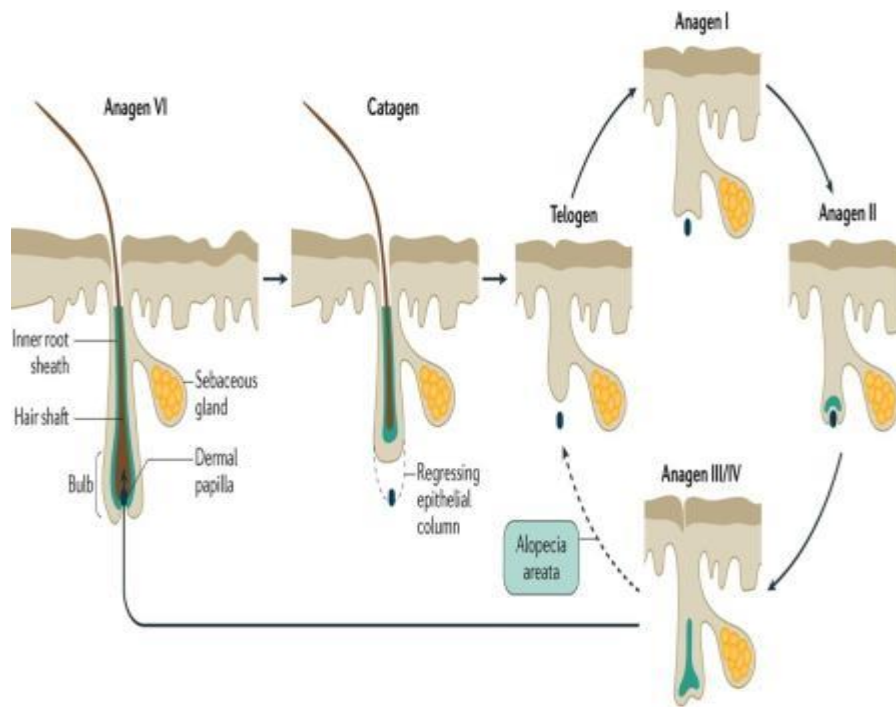


Figure (3): Pathodynamics of hair loss in alopecia areata ⁽⁴⁾.

Etiopathogenesis (Figure 3):

Genetics

The complicated genetics of alopecia areata have been studied by many different groups utilising methods like transcriptional profiling of alopecia-affected skin, candidate gene association studies, and big genome wide association analysis. Genetic research initially zeroed focused on a single gene thought to play a role in a cluster of autoimmune disorders. Type 1 diabetes mellitus, psoriasis, and alopecia areata are only few of the diseases linked to these genes ⁽¹²⁾.

The hunt for an autoimmune aetiology led to the discovery of the HLA region, which in humans encodes MHC molecules, as a major contributor to the alopecia areata phenotype ⁽¹³⁾.

One of the genome's most gene-dense areas, the HLA region on chromosome 6, encodes important immune regulators. For instance, 14 genetic loci have been linked to alopecia areata in humans through multiple GWAS investigations, many of which are known to be important in immunological function ⁽¹²⁾.

According to a paper, the primary effectors in the pathophysiology of the alopecia areata condition are CD8 cytotoxic T cells. Additionally, Janus kinase (JAK) signaling pathways are upregulated. JAK inhibitors are utilised to block the signaling pathway downstream and novel therapeutic strategies are being developed ⁽¹⁾.

Breakdown of immunoprevelage (Figure 4):

Because microglobulin and transporter of antigen processing, two components of the MHC class I pathway, have been downregulated, the proximal region of the anagen hair follicle is immune privileged because MHC class I expression is missing or expressed at extremely low levels. Because of this, it has been postulated that the hair follicle is where the immune system stores antigens for later use. Lack of MHC class II antigens, the expression of potent immunosuppressants such as transforming growth factor 1, ACTH, and MSH, the absence of intraepithelial T cells, the absence of lymphatics, and the presence of a unique extracellular matrix barrier may all contribute to impaired immune cell trafficking caused by a dearth of antigen-presenting cells ⁽⁶⁾.

Alopecia areata is caused by a number of factors, including genetic predisposition, a positive family history of the condition, monozygotic twins, hormonal factors, post-infection, vaccination, diets, and stress. These factors all contribute to the immune prevelage of the hair follicle being compromised. A biopsy reveals dense lymphocytes (T & B), with the majority being T cytotoxic cells. Mast cells and other inflammatory cells could also be present ⁽¹⁴⁾.

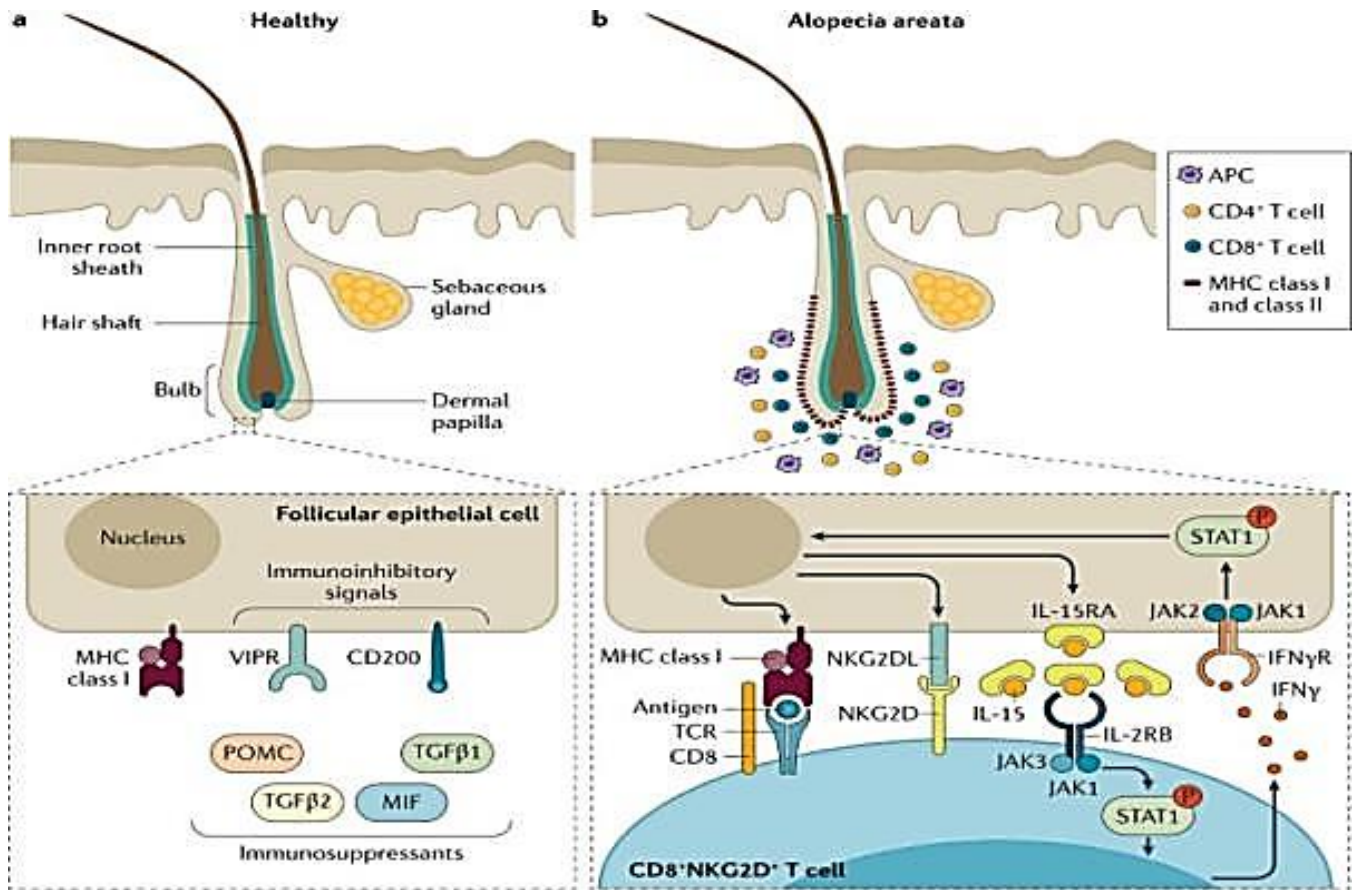


Figure (4): Breakdown of immunoprevalence in alopecia areata ⁽⁴⁾.

Autoantigen epitopes

Autoantigen epitopes may have a role in the onset of alopecia areata. Melanin, melanin-related proteins, and keratinocyte-derived antigens have all been hypothesised as potential causes of alopecia areata since white hairs typically come back after an episode and are usually spared during subsequent relapses. Patients with alopecia areata who received synthetic trichohyalin and pigmentation-related protein 2 (dopachrome tautomerase) epitopes experienced a significant increase in cytotoxic T lymphocyte responses compared to healthy control patients' peripheral blood mononuclear cells ⁽¹⁾.

Oxidative stress

Alopecia areata and other skin conditions are influenced by oxidative stress. Malondialdehyde, a marker of lipid peroxidation, and superoxide dismutase (SOD) antioxidant activity were identified in significantly higher concentrations in the blood of alopecia areata patients than in healthy controls ⁽¹⁵⁾. According to reports, whereas normal patients had no discernible reaction, 32% of alopecia areata patients had antibodies against SOD that had been harmed by reactive oxygen species. This indicates that SOD damage and oxidative stress may contribute to the development of alopecia areata. A small genetic analysis found no link between polymorphisms in SOD2 or GPX1 and alopecia areata ⁽¹⁾.

Environmental triggers

The most frequently mentioned is either physical or mental stress, such as that which follows psychic trauma. A low incidence of alopecia areata has been linked to immunizations against numerous human infections, such as the HPV, hepatitis B virus, herpes zoster, and the Japanese encephalitis virus. On the other hand, it was claimed that swine flu virus infection caused or made alopecia areata worse. A significant number of C3H/HeJ spontaneous, adult-onset mouse models of alopecia areata demonstrated that alopecia areata associated with immunisation was within the typical, anticipated incidence range, despite the addition of diphtheria and tetanus toxoids as controls ⁽¹⁶⁾.

Clinical features

The most prevalent place for sudden onset hair loss in alopecia areata is the scalp, and it most commonly affects adults. The absence of scales, erythema, or the exclamation marks that are pathognomonic for alopecia areata indicate that the skin is entirely healthy. Hair pull tests are often negative, with the exception of early active lesions near the periphery, which indicate disease activity and development ⁽¹⁷⁾.

Alopecia is categorised based on the pattern and size of the alopecia. Depending on the degree: Alopecia areata is regionalized. Totalis: total loss of scalp hair (preserved eyebrow) Universalis: total body and hair baldness (lost eyebrow) ⁽¹⁷⁾ (Figure 5).



Figure (5): Types of alopecia according to the extent ⁽¹⁷⁾.

According to the pattern (Figure 6):

Localized Marginal (ophiasis) alopecia along the margins of the scalp. Central (sisaipho): alopecia in the centre of the scalp leaving the temporal and occipital margins. Reticular: when the hair loss is extensive and the patches coalesce. Perinevoid: around halo nevus. Alopecia areata incognito (diffuse type) acute diffuse shedding in the absence of typical patches ⁽¹⁷⁾.

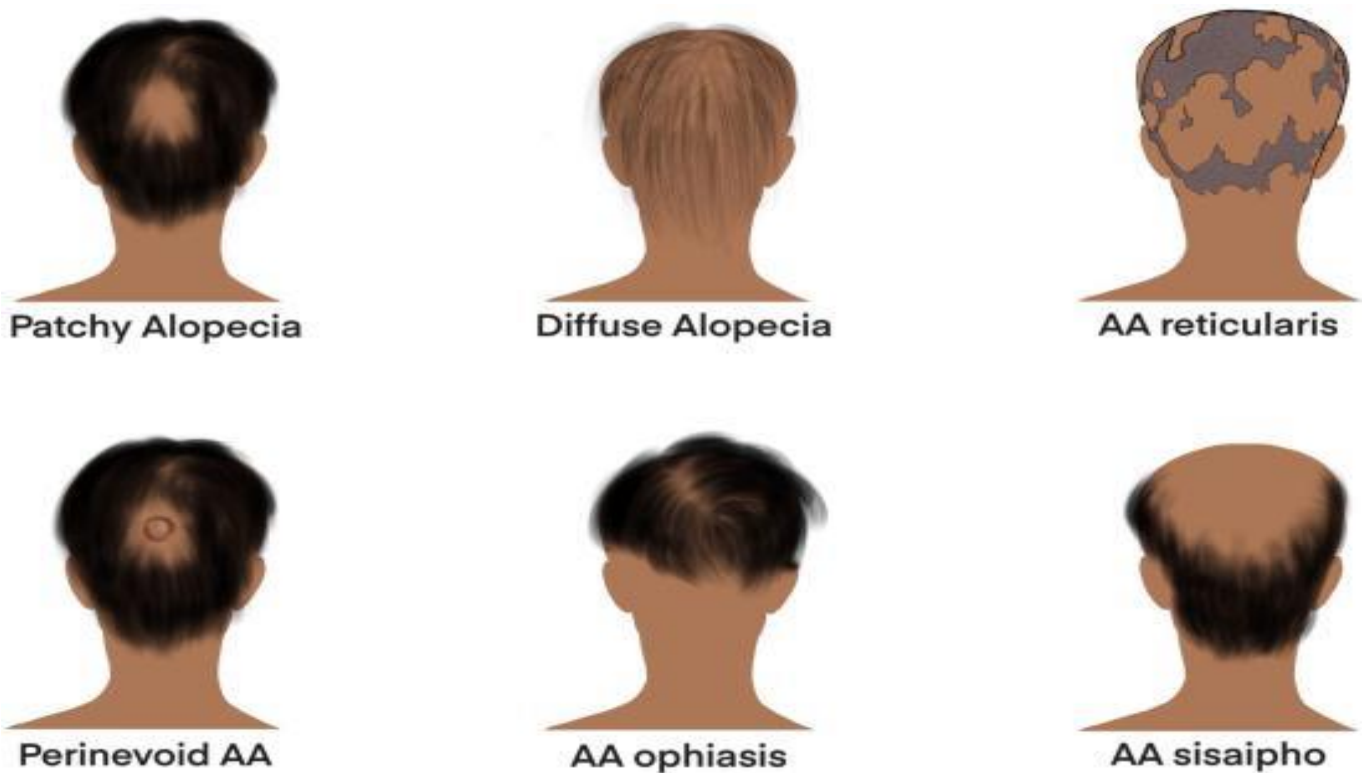


Figure (6): Types of alopecia according to pattern ⁽¹⁷⁾.

In severe cases of alopecia areata (totalis, universalis), atopy, autoimmune disease, thyroid disease, and psychological difficulties have all been implicated. Fine stippled pitting is a common feature of alopecia areata nails, but less obvious nail plate roughening with longitudinal striations may also be present (trachyonychia). The most challenging feature of the condition is often the nail dystrophy. One study including 1,000 persons with alopecia areata and nail lesions found that the prevalence of pitting was substantially higher in children than in adults ⁽¹⁸⁾.

Classification of severity

Patchy, totalis, and universalis are the traditional classifications for alopecia areata. A more thorough classification should take into account the length of the illness and the severity of the hair loss in patchy alopecia areata. The pattern should be defined by the presence of ophiasis, nail disease, patches on the trunk and limbs, and damaged beard and eyelashes. The Severity of Alopecia Tool (SALT) score was developed on the basis of these characteristics ⁽¹⁸⁾.

In order to determine the severity of alopecia areata, a tool is used to multiply the percentage of hair loss in each of the four quadrants of the scalp by the quadrants of surface area. The composite score is then calculated, with a maximum score of 100 denoting complete scalp hair loss and a minimum score of 0 denoting no hair loss ⁽¹⁹⁾.

Management

Local corticosteroids:

Immunosuppressive, a strong topical steroid such as clobetasol was used for 3 months to treat patchy alopecia areata. Intralesional steroid administration is likely the best treatment for alopecia areata that only affects certain areas of the scalp. Local cutaneous atrophy is a side effect of slow-acting steroids (such triamcinolone acetonide or hydrocortisone acetate), however it normally goes away after a few months ⁽²⁰⁾.

Stekinumab is a human monoclonal antibody that targets IL-12 and IL-23, cytokines that are significantly elevated in the skin of alopecia areata patients compared to healthy controls ⁽²⁾.

The most frequent adverse event is severe dermatitis, however the risk can be minimised with cautious drug concentration titration. Additionally common are transient occipital and/or cervical lymphadenopathy, urticaria, and vitiligo ⁽²¹⁾.

In numerous case series, a response to the immunosuppressant methotrexate has been documented. Topical tacrolimus (an immunosuppressant), despite a tiny case series suggesting a response to cyclosporine (a calcineurin inhibitor), is unsuccessful ⁽²²⁾.

Laser therapy: Patients with alopecia areata may benefit from laser therapy. Currently in use, the excimer laser (an ultraviolet (UV) laser) may provide a secure

and efficient replacement for present medical procedures ⁽²³⁾.

Psychological assistance: Many persons who suffer from severe patchy alopecia areata, alopecia totalis, or alopecia universalis do not see improvement from current medical treatments ⁽²⁴⁾.

Antibodies and biologics

Stekinumab, a human monoclonal antibody that targets these cytokines, was administered to alopecia areata patients whose skin IL-12 and IL-23 levels were much higher than those of healthy patients. Full hair regrowth was visible within a matter of weeks for this selected set of patients, and they continued to make improvements at both the 20- and 28-weeks treatment marks. Adults with plaque psoriasis can now legally be treated with secukinumab, a human IL-17A antagonist. Clinical trials of this medication also include those with alopecia areata ⁽²⁵⁾.

JAK blockers: Ruxolitinib is a JAK1/2 inhibitor that has been licenced by the FDA for the treatment of rheumatoid arthritis and myelofibrosis (tofacitinib, a pan-JAK inhibitor). Several case series and individual reports have demonstrated that patients with alopecia areata, including alopecia universalis, experienced hair growth after therapy with oral JAK inhibitors. Inhibitors of Janus kinase (JAK) include the drugs tofacitinib, ruxolitinib, and baricitinib ⁽²⁶⁾.

Stem cell approaches:

In this procedure, mononuclear cells from alopecia areata patients are isolated, given the opportunity to communicate with multipotent stem cells from human cord blood, and then released back into the patient's bloodstream. Increased production of T helper 2 cytokines and a return to a balance between Th1, Th2, and Th3 appeared to be the underlying processes ⁽²⁷⁾.

CONCLUSION

According to a paper, the primary effectors in the pathophysiology of alopecia areata condition are CD8 cytotoxic T cells. Additionally, Janus kinase (JAK) signaling pathways are upregulated. JAK inhibitors are utilized to block the signaling pathway downstream and novel therapeutic strategies are being developed. The most prevalent place for sudden onset hair loss in alopecia areata is the scalp, and it most commonly affects adults. The absence of scales, erythema, or the exclamation marks that are pathognomonic for alopecia areata indicate that the skin is entirely healthy. Hair pull tests are often negative, with the exception of early active lesions near the periphery, which indicate disease activity and development.

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- **Competing interests:** Nil.

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