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Review

Exploring Alopecia Areata: Clinical Variations, Hair Follicle Dynamics, and Treatment Perspectives

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ABSTRACT

Alopecia areata (AA) is an autoimmune disorder that primarily affects the scalp and leads to hair loss. Although its overall incidence is approximately 2%, it is commonly observed in young age groups and children. Alopecia areata has different clinical types/subtypes within itself. The hair follicle cycle consists of three phases: anagen phase, catagen phase, and telogen phase. In patients with AA, the first observed event is the rapid transition of hair follicles from the anagen phase to the catagen and telogen phases. The diagnosis of the disease is generally made clinically, supported by findings such as a positive hair-pull test or trichoscopy. Vellus hairs in the lesions are also considered a hallmark of AA. Despite the availability of many medical and non-medical treatment options for AA, only a few of them are supported by studies. In this review, we thoroughly explore the intricate domain of AA, an autoimmune disorder primarily impacting the scalp and resulting in hair loss.

Keywords: Alopecia areata, hair loss, skin disorders

Alopecia areata (AA) is an autoimmune condition primarily impacting the scalp, causing hair loss. Extensive international research has estimated the occurrence of AA to range from 0.57% to 3.8%, with a higher prevalence noted among younger individuals. The predominant age bracket for its initiation is between 21 and 40 years, trailed by the age ranges of one to 20 years, 41 to 60 years, and ultimately 61 to 80 years. Although involvement can occur in other body areas, the scalp is the most common site.[1] Moreover, male patients are more likely to be diagnosed while they are younger, whereas female patients are more likely to develop AA throughout adolescence.[2]

HAIR FOLLICLE STRUCTURE AND HISTOLOGY

Hair is a complex biological structure formed by the bonding of keratin molecules. The keratin molecules that makeup hair are proteins with different structures and molecular weights. Keratin is produced in the cytoplasm and contains amino acids such as arginine, cysteine, and tyrosine. Disulfide bonds present in keratin prevent the solubility of hair keratin in water, allowing it to remain in a stable form. Any breakage in disulfide bonds weakens the hair.[3] Hair size and color vary according to age, race, gender, and body region. They are found everywhere in the body except the palms, soles, lips, glans penis, clitoris, and labia minora. There are approximately five million hair follicles in the human body, with about 100,000 of them located in the scalp. Each hair develops from an epidermal invagination, in other words, a hair follicle. The hair follicle consists of three parts in a horizontal section, namely the cuticle, cortex, and medulla.[4]

HAIR CYCLE

Hair is not in a continuous state of growth; it goes through a cyclic phase, in addition, while hair growth is simultaneous, the individual hairs do not affect each other. After going through the last phase of growth, hair falls out, and new ones take their place. This shedding is occasionally observed, but it can be more pronounced during certain seasonal transitions. The life of a hair follicle is divided into three important

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phases: anagen (growth) phase, catagen (regression, transition) phase, and lastly, telogen (rest) phase.

The anagen (growth) phase lasts for several years, the catagen phase lasts for a few days, and the telogen phase lasts for a few months. In the anagen phase, the mature follicle's hair bulb is located deep within the dermis or subcutaneous tissue. Matrix cells are quite light and divide every 24 hours to produce hair made up of the medulla, cortex, cuticle, and inner root sheath. Furthermore, the hair growth rate is an average of 0.35 mm/day. This phase's hair is firmly attached to the hair follicle and only separates from its root when pulled forcefully.[5] Following, the catagen phase is quite short and lasts for a few days, characterized by programmed cell death. At the beginning of this phase, there is thinning of the hair in the lower part of the hair shaft, and there is a decrease in pigment. Growth abruptly halts, and the keratinized hair bulb is transported from the dermis to the epidermis. The telogen phase (resting phase) is known to last about 3-4 months in the scalp, however, due to extra and intrafollicular signals, its duration is variable. In this phase, the distal end of the follicle is just below the opening of five sebaceous glands, and it contains a club-shaped hair enclosed by the epithelial sheath. At the end of the telogen phase, hairs are shed by brushing or spontaneously, and the remaining epithelial or stem cells move deeper into the dermis towards the papilla and a new anagen phase begins.[6,7]

The hair cycle is regulated by neurons and hormones. This growth is controlled by estrogen, thyroid hormone, glucocorticoids, retinoids, prolactin, and growth hormone. Androgens have the most significant effect during this period. Hair follicles have rich innervation. In the bulge area of the hair follicle, there are numerous Merkel cells, nerve endings, and neurosecretory cells that control hair follicle proliferation.[8]

HAIR TYPES

Hair is classified into three types based on its structures and lengths:

The vellus hair: Short, thin, non-medullated hair. They are found all over the body surface except for the palms, soles of the feet, mucous membranes, and semi-mucous membranes. The length of these hairs rarely exceeds two centimeters. Following is the lanugo hair: Soft, thin, non-medullated hairs. They cover the fetus and are shed in the eighth or ninth week of gestation in newborns. And lastly, terminal hairs: Colored, thick, medullated, long hairs. Examples include scalp hair, underarm hair, and pubic hair.[9]

DYNAMICS OF HAIR LOSS

The dynamics of hair growth have changed in patients with AA. In these individuals, there is an increase in telogen hairs and an abnormal increase in the ratio of atypical hair shafts before hair loss, leading to increased fragility compared to normal hair. Under normal conditions, most hairs are in the anagen phase. However, in individuals with AA, the initial event is the rapid transition of hair follicles from the anagen phase to the catagen and telogen phases. Less affected follicles remain in the anagen phase, but they eventually produce hair shafts that progress to the telogen phase.[10]

Exclamation mark hairs are a significant characteristic of AA and are not observed in normal individuals. This hair type has a similar appearance to the root of a telogen hair, but the root is generally narrower and more easily detached. When the effects of AA begin to subside, it has been observed that hair follicles progress back toward the anagen phase.[11]

CLINICAL FEATURES

The general characteristic features of AA are shown as smooth, sharply defined, round hair patches without atrophy. When AA is examined in different clinical forms, the following characteristics are observed:

Patchy AA involves single or multiple separate or confluent (reticular) hair loss patches. Alopecia totalis (AT) leads to extensive or nearly complete hair loss on the scalp, while alopecia universalis (AU) is marked by nearly total hair loss across the entire body. Alopecia incognita is identified by a positive hair-pull test, characterized by the presence of short, regrowing hair with yellow dots, and is not associated with nail problems. Ophiasis showcases a band-like pattern of hair loss at the periphery of the scalp, particularly along the edges of the temples and occipital bones. Sisaipho denotes widespread hair loss beyond the scalp. Lastly, Marie Antoinette syndrome is recognized by the partial loss of pigmented hair, often accompanied by sudden whitening in cases of acute diffuse alopecia.[12,13]

Diagnosis

The diagnosis is typically based on clinical examination and supported by findings such as a positive hair-pull test or trichoscopy, a non-invasive

method for visualizing hair shafts and the scalp. An active disorder is characterized by yellow dots, black dots, or tapered and broken hairs. Vellus hairs in the lesions can serve as a hallmark of AA and may indicate inactive or remissive AA. In cases of uncertainty, a biopsy can be performed.[14,15]

ALOPECIA AREATA IN CHILDREN

In pediatric cases, AA constitutes an autoimmune non-scarring alopecia spectrum, where some patients exhibit small patches of hair loss on the scalp, while others may experience partial or total loss of scalp and body hair, like eyebrows and eyelashes. Limited research is available for the treatment of this disorder observed in children, and the majority of gathered information stems from studies conducted on adult cases, leading to the necessity of off-label use of medications. Generally, topical corticosteroids are the preferred first-line treatment for pediatric AA. Additionally, systemic treatments that modulate the immune system, including Janus kinase (JAK) inhibitors, are employed in this condition. However, JAK inhibitors have limited safety and efficacy data in pediatric populations. To enhance the effectiveness and safety evaluation of therapeutic options for pediatric AA, further placebo-controlled double-blind randomized studies are needed.[16]

TREATMENT

While numerous diverse treatment methods exist to promote hair growth in cases of AA, very few of these treatments have been tested through randomized controlled trials, and there is limited data on their long-term effects. Despite various guidelines and treatment options available in other countries, these options have not been approved by the Food and Drug Administration in the United States. Some patients currently respond positively to the available treatments. However, the positive response rate is lower in patients with severe AA (AT, AU, or a combination of both). Patients with AT and AU exhibit a high level of immune reactivity in controls compared to normal cases.[17]

Not all patients may require treatment or may choose not to undergo treatment. The prognosis of long-standing widespread AA is less favorable compared to the norm, and the failure rate of all currently available treatments is very high. Consequently, these patients might opt not to seek treatment or prefer cosmetic options. For many patients, the priority is to prevent ongoing hair loss. At this point, the clinician's role is to provide the patient with counseling regarding the disease's mechanism, course, available treatments, and success rates. It should be noted that psychological support might be necessary for some patients.[18]

Local Corticosteroids

A potent topical steroid (for instance, clobetasol) administered within the formulation of a cosmetic product (lotion, foam, shampoo) serves as a treatment option for patients with limited patchy AA, and it accelerates hair growth improvement in cases of mild AA. The treatment duration should be at least three months, but if there is no response after six months, the treatment should be discontinued. A rare complication is inflammation of the hair follicles.[19]

Local steroids are not effective in treating AT and AU. Among the various treatment methods, the most effective for patchy AA patients is intra-lesional steroid injection. This procedure involves using a fine needle injection or a needle-free device to administer a slow-releasing steroid (such as hydrocortisone acetate or triamcinolone acetonide) into the subcutaneous tissue of the upper skin. The goal is to stimulate hair growth improvement in the injected area. However, this procedure often requires multiple injections, and localized cutaneous atrophy is a common side effect. Fortunately, this side effect tends to improve within a few months.[20,21]

It is important to note that intralesional steroid application does not prevent AA from developing in other areas. This method is not suitable for patients with rapidly progressing patchy AA, AT, or AU. Research has indicated that after intralesional corticosteroid treatment, the levels of certain immune cells, including CD8+ T cells, CD11c+ dendritic cells, and CD1a+ Langerhans cells in and around hair follicles, decrease. Moreover, changes in gene expression have been observed, with the downregulation of several interleukin and chemokine coding genes, and the upregulation of several keratin coding genes reported after treatment. These findings suggest that these genes could potentially serve as important biomarkers for monitoring local steroid treatment in AA patients.[22]

Other substances that are suggested to be effective in patients with limited patchy alopecia, but whose benefits are uncertain, include the vasodilator minoxidil and anthralin (also known as dithranol), which have antiproliferative and anti-inflammatory effects.[23]

Systemic Corticosteroids

The long-term daily treatment approach with oral corticosteroids has been successfully used to improve hair growth in patients with extensive and rapidly progressing AA. In a partially controlled study, it has been reported that a 6-week oral prednisolone tapering regimen resulted in significant regrowth of more than 25% of hair in 30-47% of mild to severe AA patients under treatment. For most patients, continuous treatment is necessary to sustain hair regrowth. In a few case reports, positive responses have been observed in high-dose pulsed corticosteroid treatment using various oral and intravenous regimens. In the only controlled study conducted, AA patients receiving prednisolone once a week for three months were reported to have better hair growth within six months compared to the placebo group.[24]

Contact Immunotherapy

Contact immunotherapy is an effective treatment option for some patients with AA, specifically those with patchy hair loss. This therapy involves applying a strong allergen to a small area of the scalp to sensitize the patient's immune system. Later, the same allergen is applied to the patient's skin on a weekly basis, triggering a mild allergic reaction that leads to contact dermatitis. Common allergens used in this treatment include dinitrochlorobenzene, squaric acid dibutyl ester, and the widely used diphenylcyclopropenone.[25]

The exact mechanism of how contact immunotherapy works is not completely understood. It's believed that the antigens used in this therapy can induce 'antigenic competition,' redirecting certain immune cells away from the hair follicles, for instance, can lead to the displacement of CD4+ T cells from the perifollicular area.[26] Another proposed mechanism involves stimulating certain immune cells in the skin. Although the success rates vary significantly, ranging from 9% to 87%, approximately 20-30% of patients experience hair regrowth without needing to wear wigs.[27]

Patients with more extensive hair loss tend to have less favorable responses. Negative factors predicting success include nail abnormalities, early onset of hair loss, and a family history of the condition. If there is no response after six months of treatment, it is typically discontinued. In a study, significant hair regrowth was observed in 30% and 78% of patients respectively at six and 32 months after completing the treatment. This suggests that long-term treatment is often necessary to achieve positive results. However, the response rate for patients with complete hair loss on the scalp (AT) or complete hair loss all over the body (AU) was only 17%. Among patients who successfully completed the treatment, 62% experienced a recurrence of hair loss.[27,28]

Despite more than 30 years of use, long-term side effects of contact immunotherapy have not been observed. The most common side effect is severe dermatitis, but careful adjustment of the drug concentration can reduce this risk.[29] Temporary enlargement of lymph nodes in the neck or back of the head is commonly seen during treatment and continues as long as the treatment is ongoing.[27] Urticaria (hives) and vitiligo are less common side effects. In patients with pigmented skin, changes in skin pigmentation, either darkening (hyperpigmentation) or lightening (hypopigmentation), can occur.[30-32] Sensitivity among healthcare workers is a significant concern, and avoiding contact with the applied allergen is important.

Other Treatments

Response to methotrexate, an immunosuppressant, has been reported in several case examples. While it has been suggested that cyclosporine, a calcineurin inhibitor, may elicit a response based on a small case series, its use is not considered appropriate due to potential side effects.[33] Moreover, the effectiveness of topical tacrolimus, an immunomodulator, has been shown to be ineffective. A study using etanercept revealed that it is not effective in the treatment of moderate and severe AA. Additionally, the development of AA has been observed in patients with autoimmune disorders under treatment with adalimumab, infliximab, or etanercept. Small, randomized trials have demonstrated that efalizumab and alefacept offer no benefit in AA.[34]

NON-MEDICAL TREATMENTS

Laser Therapy

In contrast, laser therapy shows positive results in patients with AA. The excimer laser is commonly used and is considered a safe and effective alternative to medical treatments. Randomized controlled trials are needed to confirm its superiority over medical treatment. Preclinical experiments using a mouse model showed that laser comb did not exhibit effectiveness for AA. Uncontrolled studies have shown success rates of 60-65% for all types of oral or topical psoralen, localized or whole-body ultraviolet A (UVA) exposure phototherapy in AA patients.

However, relapse rates are high, and treatment must be continuous to maintain hair growth, leading to a high cumulative UVA dose.[35,36]

Cosmetic Strategies

Female patients with widespread AA can use wigs, hairpieces, or headscarves. While some patients prefer wigs, men often prefer to shave their heads. The use of semi-permanent tattoos is a good alternative to conceal eyebrow loss.[37]

Psychological Support

Many patients with AA, AT, and AU experience unsuccessful outcomes with medical treatments. Clinically significant depression, job loss, social isolation, and other symptoms can be observed in individuals with AA. The clinician plays a crucial role in addressing these issues. Managing body image concerns may require assistance from a clinical psychologist or another professional. The National Alopecia Areata Foundation and Alopecia UK are some organizations that can provide assistance. Coping with AA can be more challenging for children than adults. In necessary cases, pediatric patients should be referred to a pediatric clinical psychologist.[38]

In conclusion, AA is a prevalent condition among the young population, characterized by the involvement of the scalp and various parts of the body. Despite the lack of sufficient studies, there are existing treatment methods in the literature for diagnosing AA using various diagnostic approaches.

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