The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2897-2903

Alopecia Areata: An Overview of the Disease and its Genetic Basis: Review Article

Raghda Atef Abd Elshafy*[1], Naglaa Ali Khalifa[2], Rasha Mohamed Besher[3], Howyda Mohamed Ebrahim[1], Mahmoud Yousry M. Abdel Mawla[1]

Departments of [1]Dermatology, Venereology, and Andrology and
[2]Clinical Pathology, Faculty of Medicine, Zagazig University, Sharkia, Egypt
Department of [3]Dermatology, Al-Ahrar Teaching Hospital, Sharkia, Egypt

***Corresponding author:** Raghda Atef Abd Elshafy, **Mobile:** (+20)01145449382, **Email: raghdaatef333@gmail.com**

ABSTRACT

Background: Alopecia areata (AA) is a frequent, reversible kind of hair loss. It is commonly seen as patchy regions of full hair loss on the scalp and other body parts that might lead to complete loss of all body hair. The condition is characterized by localized inflammatory lesions with perifollicular T-cell infiltrates, demonstrating the importance of local cytokine generation in the formation of patchy hair loss. IL-1β is a major inhibitor of hair development in vitro. Its impact is blocked by the interleukin-1 receptor antagonist, IL-1ra.

Objective: To review the epidemiology, clinical characteristics, pathogenesis, and associated genetic factors and the emerging therapeutics for AA in this review article. Greater knowledge of the disease pathophysiology may contribute to establishing novel medicines that are more targeted and effective against AA.

Methodology: The databases were searched for articles published in English in 3 databases [PubMed – Google scholar science direct] and Boolean operators (AND, OR, NOT) had been used such as [Alopecia Areata AND Genetic Polymorphisms OR Overview] and in peer-reviewed articles between January 2001 and May 2022.

Conclusion: Comprehensive understanding of the genetic basis of AA may mediate an efficient therapeutic approach for managing and treating this life quality affecting condition.

Keywords: Alopecia Areata; Genetic; Polymorphisms.

INTRODUCTION

Alopecia areata is characterized by patchy hair loss and T-cell infiltration at the perifollicular and intrafollicular levels. The relationship between AA and autoimmunity, particularly thyroid problems, pernicious anemia, and vitiligo, is well-established, and AA is often considered an autoimmune illness [1].

A family history of AA affects up to 40% of those who suffer from the condition. It has been established that the illness has a hereditary component [2]. HLA Class I alleles A28, B12, B13, B18, and B27, have been linked to alopecia areata; however, HLA Class II alleles DR4, DR11, DPw4, DQw3, DQw7, and DQw8 are regarded more significant. People with severe illness and an early start had a higher relative risk of disease for HLA DR5 (RR=3.14, P 0.01), and the significance of HLA genes was verified in the sole family investigation to date [3]. Nevertheless, HLA by itself could not describe the complete genetic foundation of AA, and evidence would suggest the existence of an additional alopecia areata locus on chromosome 21 [4]. As demonstrated for systemic lupus erythematosus (SLE), interaction among HLA and other loci is likely necessary for the illness phenotype.

As an important pro-inflammatory mediator, Interleukin-1 (IL-1) is a key cytokine in recruiting inflammatory cells such as T-lymphocytes, neutrophils, and macrophages to inflamed tissues [5]. Additionally known to suppress hair development *in-vitro* are IL-1, IL-1, and TNF-α [6]. These 3 cytokines have comparable effects on the morphology of cultured explant hair follicles, leading to a dystrophic anagen pattern defined by condensing of the dermal papilla and disruption and aberrant keratinization of the pericortical cells of the hair matrices. These characteristics resemble the follicular pathophysiology of AA, making the genes encoding those cytokines potential genes for AA. At least 2 agonist compounds, IL-1α and IL-1β, plus a structurally similar receptor antagonist molecule, IL-1ra, make up the IL-1 system. IL-1ra is a strong anti-inflammatory chemical because it binds to the type 1 IL-1 receptor but does not transduce a signal [5].

Variations of IL1RN are related to the intensity of various inflammatory /autoimmune disorders. Previous research established a link between the unique IL1RN VNTR allele and Alopecia Universalis, the most severe type of AA [7]. Using additional markers inside the IL1RN gene and the novel IL1RN analog, IL1L1, a recent study demonstrated a high connection between AA severity and the IL1RN gene [4].

Etiopathogenesis*:*

Etiopathogenesis of alopecia is unknown. Alopecia areata is a symptom and a disease caused by various, very complex etiological factors in persons with positive individual and family history. The etiology of AA is T-cell-mediated autoimmunity, which mostly affects genetically susceptible individuals. In addition to disturbances in immune function, illness progression is triggered by complex interactions among predisposing genetic and environmental variables. Also speculated are perifollicular nerves and vasculature, viruses, trace element changes, endocrine problems, and thyroid dysfunction. There are speculations that an imbalance of trace elements might precipitate the beginning of AA [8].

Genetic factors:

There is substantial evidence that the pathophysiology of AA has a genetic foundation.

Received: 23/1/2022
Accepted: 22/3/2022

However, there is no direct link between the phenotype and genotype in' simple' Mendelian inheritance. Therefore, hair loss in AA is a "complex characteristic"; it is multifactorial and polygenic. Unquestionably, genetic complexity explains the clinical variability found in AA. Support for a genetic etiology of AA is mostly based on increasing illness rates among patients' relatives [9].

Ten to forty-two percent of AA patients report at least one first-degree compared with a positive family history. Patients with early-onset illness are more likely to have a family history of AA, with 37 percent of individuals who had their first patch before the age of 30 having a family history of AA compared to 7.1% of patients whose disease started after the age of 30. Higher concordance among monozygotic twins compared to dizygotic twins demonstrates that genotypic similarity among identical twins is at least partially responsible for the condition [9].

According to gene association studies, multiple HLA class I (A, B, and C) alleles confer AA susceptibility in various AA sufferers' cohorts.

The bottom line is: vulnerability and illness severity are most likely determined by hereditary variables. Polygenic rather than single-gene abnormalities are most likely to blame for AA. Investigating how environmental variables may have triggered the disease is ongoing [10].

Interleukin-1b gene polymorphism in alopecia areata:

In vitro studies have shown that IL-1a inhibits hair development. It has a comparable impact on cultured explant follicle shape, which results in a dystrophic anagen pattern, with condensed dermal papilla and disruption and aberrant keratinization of the hair matrix cells. In terms of the follicular pathology of AA, the genes encoding this cytokine are a possible source of the disease's gene expression [6].

One of the most effective hair loss inducers, IL-1, is also a strong inhibitor of human hair development in vitro. Researchers have shown that the expression of type I IL-1 receptor, which is involved in signal transduction, increases dramatically when the spontaneous catagen phase of the mouse hair cycle begins, according to **Hoffman *et al.*** [11]. As Groves *et al.* found, transgenic mice overexpressing IL-1a in the epidermis suffer from AA-like hair loss.

Overexpression of IL-1 is seen in AA-affected scalps, especially in the early stages of the condition, whereas IL-1-receptor antagonist and IL-1a polymorphisms dictate disease incidence and severity. Clinically, individuals who lack IL-1 receptor antagonists due to gene polymorphisms are more likely to worsen the condition. In contrast, those with significant AA hair loss have a higher frequency of the allele 2 of the IL-1 receptor antagonist gene, the natural antagonist of IL-1 [12].

Alopecia Universalis, the most severe form of alopecia areata, has been linked to an uncommon allele of the IL1RN VNTR, according to **Tarlow *et al.*** [7]. It has been shown that the impact of IL1- and its antagonist, IL-1 receptor antagonist, on cultured hair follicles can be prevented by adding the IL-1 receptor antagonist. IL-1 gene polymorphisms may also play an excessive IL-1 release, resulting in a more fast and aggressive illness progression.

There is a high correlation between the IL-1 +3953 polymorphism allele 2 and elevated levels of IL-1 production in individuals with severe forms of the alopecia areata as demonstrated by **Galbraith *et al.*** [13]. Researchers discovered that IL-1 loci and immunoglobin light chain loci work together to greatly increase a person's vulnerability to the disease.

IL-1b production is affected by IL-1b genotypes for the indicator IL1B+3954. When it comes to IL-1b production, the IL1A+4845 polymorphism was chosen by **Hulkkonen *et al.*** [14] since it has 100 % linkage disequilibrium with the IL1A-889 polymorphism. Disequilibrium exists between IL1A+4845 and IL1B+3954, indicating a significant connection between the two genes. IL1B)511 and these 2 markers have a weak linkage disequilibrium.

The involvement of the IL-1 system in AA was examined by **Tazi-Ahnini *et al.*** [4]. There is no connection between IL1B511 or IL1B+3954 genotypes and the total dataset, illness severity, or age of onset.

AlFadhli and Nanda [15] studied the impacts of 2 different polymorphisms in the interleukin-1 (IL-1) gene [SNPs 511 and +3953] and a variable number of tandem repeat (VNTR) in the interleukin-1 receptor antagonist (IL-1RN) gene on the vulnerability and intensity of AA in Kuwaiti peoples. IL-1 SNPs C511T, C+3953T, and IL-1RN VNTR were evaluated in 96 alopecia sufferers with patchy (P), semiuniversalis (SU), and Universalis (U) disease severity, as well as in one hundred ethnically matched normal participants. To determine genotypes, a polymerase chain reaction was carried out, which was then accompanied by restriction fragment length polymorphism and direct DNA sequencing. While compared to the severity-based AA cases, the IL- SNP C511T was significantly linked. CC was 50 percent more common in U instances than in P or SU. There was a considerable difference between P and SU compared to U. IL-1 511CC genotype carriers had a higher chance of developing severe AA than those with genotype CT. IL-1RN VNTR revealed four alleles and genotypes in AA sufferers (1/1, 1/3, 1/4, and 2/2) but only 2 in normal (1/1 and 1/3). IL-1RN VNTR showed both genotype and allelotype relationships with AA. IL-1 and IL-1RN VNTR were shown to be substantially linked with alopecia areata susceptibility. The severe AA type is associated with the IL- C511T allele C.

Shaarawy *et al.* [16] investigated the probable relationship of IL-1b-C-511T and C+3953T Single Nucleotide Polymorphisms (SNP) with AA and determined that these SNPs play no etiological function in the Egyptian AA suffers analyzed.

Immunologic factors:

Strong direct and indirect evidence supports the autoimmunity as the cause of AA. Ample evidence shows that AA is an organ-specific, autoimmune disease that targets hair follicles, even though the precise etiology of this prevalent ailment has not been determined. The autoantibody reaction is diverse and targets several anagen phase hair follicle structures. Nevertheless, the antigenic target(s), mechanisms, and autoimmunity outcomes in AA are unknown [17]. AA is a disease fueled by inflammation and is probably an autoimmune condition [18].

Cellular immunity:

There is mounting evidence that AA is a tissue-specific autoimmune disorder. Lymphatic infiltration around and inside hair follicles is AA's most distinguishing histological feature. During an active illness, hair loss coincides with infiltration of activated CD4+ cells around the hair follicles and infiltration of CD8+ cells within the hair follicles. Due to the cytotoxic nature of most CD8+ T lymphocytes, their presence within hair follicles can readily impede hair development. Activated cytotoxic T lymphocytes in alopecia areata release several chemicals, such as tumor necrosis factors and granzymes; such molecules might cause apoptosis in alopecia areata-affected hair follicle cells' normal functioning [19, 20].

Immunosuppressive medications, including systemic corticosteroids and cyclosporine, and immunotherapy with touch sensitizers positively impact AA. Also, AA has been linked to several autoimmune illnesses, including autoimmune thyroiditis and vitiligo [19]. Macrophages and Langerhans cells have infiltrated the dystrophic hair follicles, as have other antigen-presenting cells.

Humoral immunity:

The existence of autoantibodies specific to hair follicles in AA sufferers indicates that AA is an autoimmune disease. The concentration of hair follicle-specific Ig-G antibodies is elevated in the peripheral blood of AA individuals, and it is located along the border of active lesions and the periphery of hair follicles. Some of these serum antibodies have been reported to bind to keratin 16 and hair follicle-specific trichohyalin. Nevertheless, the specificity of hair follicle autoantibody targets might vary considerably across AA patients [20].

Antibodies against hair follicle antigen with a high titer can range from 1 to 10,000 in humans with AA. Antibody titers are reduced by successful therapy of AA. Such antibodies can also be utilized to evaluate immunologic specificity in AA since they could be collected simply, and antibody specificities may be measured more easily than T cell specificities. This has the potential to be a valuable method for studying the epitope dissemination and development of the AA immune response [21].

Cytokines:

Cytokines and other chemicals that coordinate cyclical hair development plays a critical part in the progression of alopecia areata's etiology. Interferon-(IFN-) is the most prominent cytokine reported to be abnormally produced in alopecia areata via a CD4+ Th1-mediated response. According to human research, it is generated by perifollicular or follicular antigen-presenting cells and, among other effects, inhibits the capacity of dermal papilla cells to sustain anagen hair development. Serum levels of IFN- have been demonstrated to be considerably greater in individuals with alopecia totalis or alopecia Universalis relative to controls. However, there is no substantial variation among individuals with localized AA and people with greater widespread types [22].

It is widely recognized that tumor necrosis factor-(TNF-) plays a significant part in the etiology of AA. TNF-, along with numerous other cytokines, is generated in epidermal keratinocytes and is a particularly powerful growth inhibitor. Th1 cytokines IFN-, IL-2, IL-12, and TNF also have been identified in the sera and lesion biopsies of AA sufferers [22].

Environmental factors:

Environmental variables might have a role in the development of AA. These may collectively determine the disease's true beginning, the pattern of hair loss, and intensity. Nevertheless, the specific environmental stimuli necessary for AA expression remain unknown [23].

Emotional stress:

Psychological variables might also have a part in the development of AA, in addition to autoimmunity. Acute psychotrauma, stressful experiences, and unfavorable familial situations have been linked by certain researchers to the start of AA. Not unexpectedly, AA sufferers have additional symptoms. They are more likely to develop specific mental problems such as severe depression, generalized anxiety disorder, social phobia, or paranoid disease [24].

The stress-induced release of neuropeptides from peripheral nerves has been reported in the skin. An elevation of substance P (SP)-immunoreactive nerve fibers has been found near damaged hair follicles in AA individuals. AA is believed to be caused by the immunomodulatory features of SP, including mast cell degranulation, activation of pro-inflammatory cytokines and chemokines, etc. [25].

Infection:

AA was thought to have a possible infectious etiology, but no persistent microbial agent has been found in patients [26]. The claimed correlations among microorganisms like CMV and AA might be explained by molecular mimicry. Thus, microorganisms encoding epitopes that mimic hair follicle peptides may induce the activation of autoreactive T lymphocytes resulting

in autoimmune alopecia (AA), despite the absence of experimental data to validate this concept [17]. **Boni *et al.*** [27] observed an increased prevalence of helicobacter pylori in AA patients; however, **Rigopoulos *et al.*** [28] showed no increase in Helicobacter pylori prevalence in AA patients.

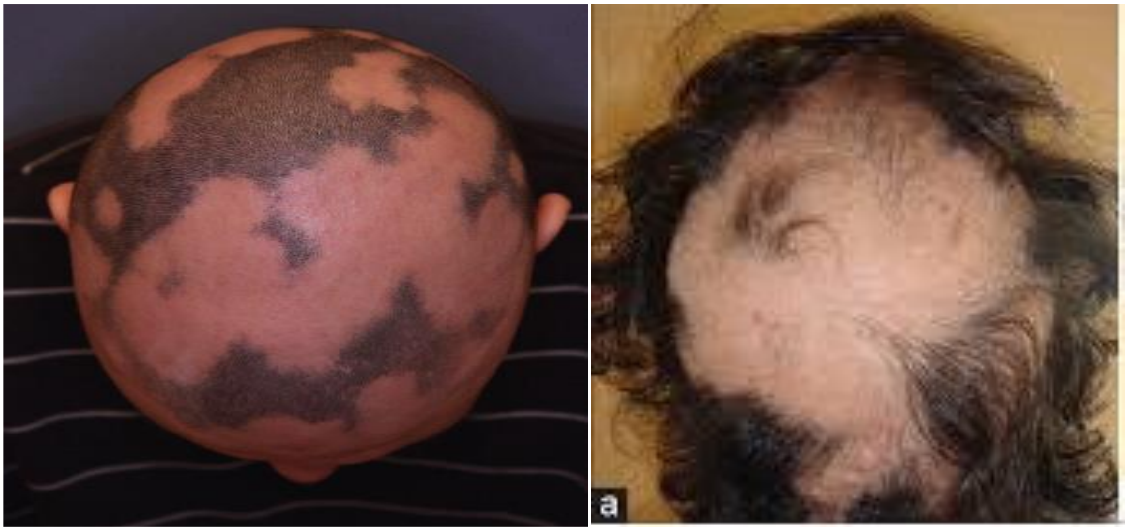
Chemical agents:

Boron is commonly utilized in industrial products, primarily as the salt borax. Systemic exposure (e.g., ingestion) or dermal exposure to boron has been correlated with, among other signs, reversible toxic alopecia [29]**.**

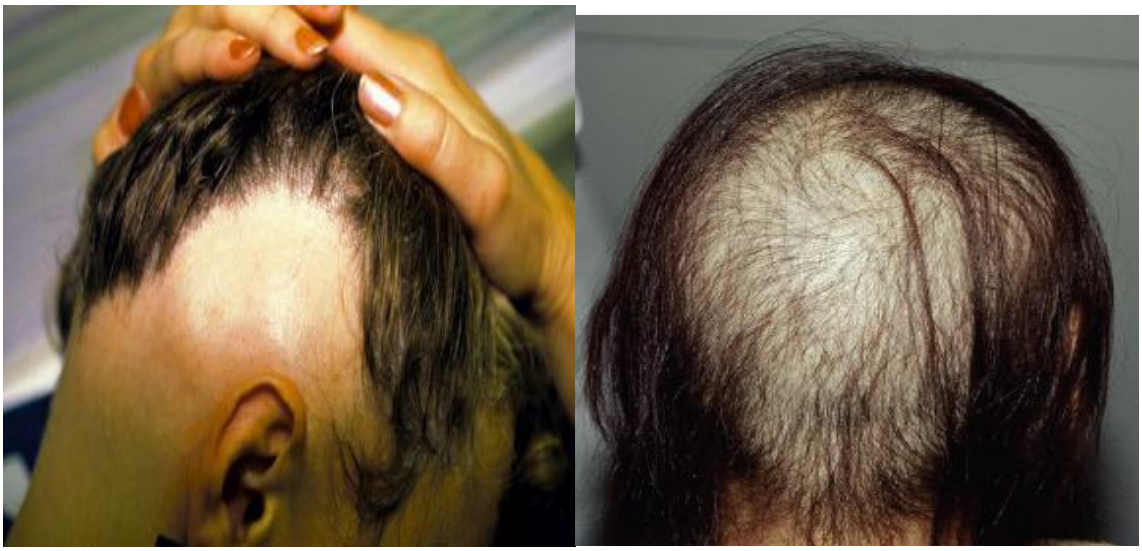
Clinical picture:

AA is distinguished by the abrupt emergence of circular or oval patches of non-scarring hair loss, accompanied by spontaneous remissions and exacerbations. The patches are well-defined, may have a little pinkish color, and occasionally contain exclamation point-shaped hairs along their margins. Exclamation point hairs are short, broken hairs with a wider distal portion than the proximal segment. The affected skin is typically smooth and nearly always completely hairless [19].

Scalp and body hair, including eyebrows, eyelashes, beard, axillary hair, and pubic hair, as well as the entire body, can be affected by alopecia areata. However, the scalp is the most prevalent site (90 %)**.** Before hair loss occurs, a few people may have pruritus, burning feelings, or discomfort, but this is uncommon. In active disease, when alopecia patches are growing, a positive hair pull test may be observed around the lesions' periphery. Nail abnormalities are another clinical sign of alopecia areata that might precede or follow the development of the illness and often remit spontaneously but may linger for a long time after the complete hair restoration [30].



AA reticularis. **AA sisiapho type.**



AA ophiasis type. **AA diffuse type.**

Figure (1): Clinical types of AA[30].

Table (1): The features of the various AA clinical subgroups are summarized below.

Alopecia Arata's subtypes	Morphological characteristics	Onset	Response to therapy	Direction and prediction
Localized Types				
Patchy AA	Well-demarcated round or oval patches of alopecia	Any age, but before 20years in >50%	Effective; complete resolution in>50%	Relatively good, although recurrence is often noted
ophias	Band-like pattern: alopecia extending along posterior occipital and temporal scalp margin	Any age, not specific	Unsatisfactory; poor response	Poor, recurrence common
sisiapho	The opposite of ophiasis type, hairs are lost centrally and spared at the margins of the scalp	Any age, not specific	Unsatisfactory; poor response	Poor, recurrence common
Extensive Types				
AT , AU	Loss of all scalp terminal hairs; loss of all scalp and body hair	Any age, but earlier than other types of AA	Unsatisfactory; response (+) in <50% of patients and complete recovery in <10%	Poor; rare recovery and tend to worsen over time
ADTA	Initial diffuse hair loss and rapid progression to total baldness	After the age of 20 (around 30 y), Female predominance	Patients experienced hair regrowth within about 6 months, without regard to the method of treatment	Good; rapid recovery even without treatment

Associated abnormalities:

In addition to atopic dermatitis, Hashimoto's thyroiditis, hypothyroidism, endemic goiter, Addison's disease, pernicious anemia, SLE, diabetes mellitus (DM), and other forms of autoimmune disease, AA is commonly seen in conjunction with other forms of autoimmunity**.**

Nail changes: AA may be connected with nail alterations. Ten to sixty-six % of individuals undergo nail alterations regularly. Alterations may be detected in a single, several, or all of the nails. The most prevalent form of nail degeneration noticed in AA is pitting. Also seen are longitudinal ridges and thickening. Nail dystrophy may linger for years following the resolution of AA **[19].**

Thyroid autoimmunity: autoimmunity of the thyroid may be related to AA, with a frequency in 8% and 28% of patients. The presence of thyroid autoantibodies does not correlate clinically with the severity of AA. Vitiligo may be an additional significant relationship, with a 3 to 8% occurrence in AA individuals **[23]**.

Atopic dermatitis: ~ 9 to 26% of AA patients have atopic dermatitis, which is higher than the frequency in the general population. The severity of concomitant atopic disorders may be a more important factor in defining the severity of AA than the simple existence of an atopic condition alone. Some writers have shown atopy to be an unfavorable predictor of AA **[26].**

Emotional stress and psychiatric disease*:* There is an elevated frequency of anxiety, personality disorders, depression, and paranoid disorders ranging from 17 to 22 percent of patients, and the lifetime prevalence of mental illnesses was predicted to be 74% in patients with AA. Psychiatric issues can affect both children and adults. There is no correlation between the severity of the mental disease and AA **[31].**

Down syndrome*:* ~ 6-8.8 % of people with Down's syndrome have AA, but only 0.1% of individuals with AA had Down syndrome. The significant prevalence of AA in patients with Down syndrome shows that AA might be linked to chromosome 21 genetically. The polygenic theory for AA has also been described **[32]**.

Down syndrome, Addison disease, pernicious anemia, psoriasis, lupus, celiac disease, ulcerative colitis, and multiple sclerosis are related to AA. These rare autoimmune illnesses are much more likely to be linked to AT/AU **[33].**

Differential diagnosis:

AA is clinically defined by areas of non-scarring hair loss with 'exclamation point hairs. Additional reasons for nonscarring alopecias must be considered (androgenic alopecia, telogen effluvium, trichotillomania, and traction alopecia) **[18].**

Tinea capitis and trichotillomania are the most critical things to rule out in pediatric patients. Tinea capitis could be distinguished by the presence of at least modest scaling or inflammation. Trichotillomania might involve lesions with uneven or unusual shapes. Lesions have a rough texture because of the existence of broken hairs of various lengths, in contrast to the smooth surface of AA **[23]**.

When diffuse alopecia areata is evaluated, telogen effluvium, syphilitic alopecia, and androgenic alopecia

must be ruled out. It may be distinguished readily based on its distinctive clinical characteristics, laboratory results, and inflammatory nature, as shown in Table 2**.**

Table (2): Differential diagnosis of alopecia areata (clinically) **[18].**

	Clinically
Alopecia areata	-Usually patchy but can be generalized -Exclamation-point hairs -Abrupt onset; often waxes and wanes with relapses -Prominent shedding -Onset at any age; most have their first patch before age 20 -Hair pull test: Positive; dystrophic anagen and telogen hairs
Androgenetic alopecia	-Focal balding pattern. -Generalized -Gradual onset with progression -Thinning with or without bare patches. - Minimal Shedding -Onset at puberty or older -Hair pull tests are usually negative
Telogen effluvium	- Generalized Excessive shedding of the normal telogen club hair - Onset is abrupt, often with trigger factors most commonly occur 3-6 months following pregnancy, parturition, surgery, dieting, drugs -Thinning with no bare patches -Onset at any age, but usually not childhood -Hair pull test: Positive; telogen hairs
Trichotillomania	-Obsessive-compulsive disorder of plucking hair from the scalp, eyelashes, or brows -Irregular patches of alopecia containing the hair of varying length
Syphilitic alopecia	-May have a typical moth-eaten appearance on occipital scalp -May occur as generalized thinning of hair -May resemble alopecia areata

Treatment modalities:

Due to psychological stigmatization, it is difficult to dispute the medical care and therapy of patients who suffer from a specific form of AA. AA is now treated with topical and intralesional corticosteroids, topical minoxidil solution, topical anthralin, and contact sensitizers. The choice to systematically treat AA relies on the severity of alopecia, the individual's age, general health, and the individual's motivation and physiological stress. Systemic therapies might be explored as a medical option for people with rapidly advancing diseases, significant hair loss, and therapy-resistant instances. Immunosuppressant medicines such as cyclosporine, systemic corticosteroids, methotrexate, and sulfasalazine are systemic treatments for AA **[34].**

AA has been treated with various treatment techniques with different success and safety profiles. Several therapies could cause new hair growth in AA, but they do not alter the disease's progression. AA patches respond better to therapy than alopecia totalis/Universalis. Regrettably, none of these substances have therapeutic or preventative properties. In addition, most of these treatment modalities have not undergone randomized, controlled trials, and, except for topical immunotherapy, there are few published studies on long-term effects. The treatment approach is tailored to the patient's age and illness severity **[35]**.

CONCLUSION

A comprehensive understanding of the genetic basis of AA may mediate an efficient therapeutic approach for managing and treating this life quality affecting condition.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally to the study.

REFERENCES

1. **Gilhar A, Etzioni A, Paus R (2012):** Alopecia areata. N Engl J Med., 366:1515–1525.
2. **Alkhalifah A, Alsantali A, Wang E *et al.* (2010):** Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. J Am Acad Dermatol., 62:177–188.
3. **de Andrade M, Jackow C, Dahm N *et al.* (2001):** Alopecia areata in families: association with the HLA locus. The journal of investigative dermatology. Symposium proceedings, 4(3): 220–223. https://doi.org/10.1038/sj.jidsp.5640215
4. **Tazi-Ahnini R, McDonagh A, Cox A *et al.* (2001):** Association analysis of IL1A and IL1B variants in alopecia areata. Heredity, 87(Pt 2): 215–219.

5. **Dinarello C (2003):** Biologic basis for interleukin-1 in disease. Blood, 87(6): 2095–2147.
6. **Philpott M, Sanders D, Bowen J *et al.* (2004):** Effects of interleukins, colony-stimulating factor and tumor necrosis factor on human hair follicle growth in vitro: a possible role for interleukin-1 and tumor necrosis factor-alpha in alopecia areata. The British Journal of Dermatology, 135(6): 942–948.
7. **Tarlow J, Clay F, Cork M *et al.* (2002):** Severity of alopecia areata is associated with a polymorphism in the interleukin-1 receptor antagonist gene. The Journal of Investigative Dermatology, 103(3): 387–390.
8. **Bhat Y, Manzoor S, Khan A *et al.* (2009):** Trace element levels in alopecia areata. Indian Journal of Dermatology, Venereology, and Leprology, 75(1): 29–31.
9. **Dudda-Subramanya R, Alexis A, Siu K *et al.* (2007):** Alopecia areata: genetic complexity underlies clinical heterogeneity. European Journal of Dermatology, 17(5): 367–374.
10. **Karadag A, Tutal E, Ertugrul D *et al.* (2012):** Serum holotranscobalamine, vitamin B12, folic acid and homocysteine levels in patients with vitiligo. Clinical and Experimental Dermatology, 37(1): 62–64.
11. **Hoffmann R, Wenzel E, Huth A *et al.* (2002):** Cytokine mRNA levels in Alopecia areata before and after treatment with the contact allergen diphenylcyclopropenone. The Journal of Investigative Dermatology, 103(4): 530–533.
12. **Hoffmann R (2003):** The potential role of cytokines and T cells in alopecia areata. The Journal of Investigative Dermatology. Symposium Proceedings, 4(3): 235–238.
13. **Galbraith G, Palesch Y, Gore E *et al.* (2005):** Contribution of interleukin 1beta and KM loci to alopecia areata. Human Heredity, 49(2): 85–89.
14. **Hulkkonen J, Laippala P, Hurme M (2008):** A rare allele combination of the interleukin-1 gene complex is associated with high interleukin-1 beta plasma levels in healthy individuals. European Cytokine Network, 11(2): 251–255.
15. **Alfadhli S, Nanda A (2014):** Genetic analysis of interleukin-1 receptor antagonist and interleukin-1β single-nucleotide polymorphisms C-511T and C+3953T in alopecia areata: susceptibility and severity association. Clinical and Experimental Medicine, 14(2): 197–202.
16. **Shaarawy E, Abd El-Hay R, Samir N *et al.* (2016):** Lack of association between interleukin-1b gene polymorphisms and alopecia areata: A case-control study. Med J Cairo Univ., 84(2): 197-201.
17. **Alexis A, Dudda-Subramanya R, Sinha A (2009):** Alopecia areata: autoimmune basis of hair loss. European Journal of Dermatology, 14(6): 364–370.
18. **Stefanato C (2010):** Histopathology of alopecia: a clinicopathological approach to diagnosis. Histopathology, 56(1): 24–38.
19. **Gilhar A, Kalish R (2006):** Alopecia areata: a tissue-specific autoimmune disease of the hair follicle. Autoimmunity Reviews, 5(1): 64–69.
20. **Wang E, McElwee K (2011):** Etiopathogenesis of alopecia areata: Why do our patients get it?. Dermatologic Therapy, 24(3): 337–347.
21. **Norris D (2009):** Alopecia areata: current state of knowledge. Journal of the American Academy of Dermatology, 51(1): 16–17.
22. **Gregoriou S, Papafragkaki D, Kontochristopoulos G *et al.* (2010):** Cytokines and other mediators in alopecia areata. https://doi.org/10.1155/2010/928030
23. **Alkhalifah A, Alsantali A, Wang E *et al.* (2010):** Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. Journal of the American Academy of Dermatology, 62(2): 177–190.
24. **Willemsen R, Vanderlinden J, Deconinck A *et al.* (2006):** Hypnotherapeutic management of alopecia areata. Journal of the American Academy of Dermatology, 55(2): 233–237.
25. **Kim H, Cho D, Kim H *et al.* (2006):** Immunoreactivity of corticotropin-releasing hormone, adrenocorticotropic hormone and alpha-melanocyte-stimulating hormone in alopecia areata. Experimental Dermatology, 15(7): 515–522.
26. **Huang K, Mullangi S, Guo Y *et al.* (2013):** Autoimmune, Atopic, and Mental Health Comorbid Conditions Associated with Alopecia Areata in the United States. JAMA Dermatol., 13: 1-5.
27. **Böni R, Burg G, Wirth H (2007):** Helicobacter pylori und Hauterkrankungen--ein (noch) ungebrochener Mythos? [Helicobacter pylori and skin diseases--a (still) intact myth?]. Schweizerische medizinische Wochenschrift, 130(37): 1305–1308.
28. **Rigopoulos D, Katsambas A, Karalexis A *et al.* (2011):** No increased prevalence of Helicobacter pylori in patients with alopecia areata. Journal of the American Academy of Dermatology, 46(1): 141-46.
29. **Beckett W, Oskvig R, Gaynor M *et al.* (2006):** Association of reversible alopecia with occupational topical exposure to common borax-containing solutions. Journal of the American Academy of Dermatology, 44(4): 599–602.
30. **Kasumagic-Halilovic E, Prohic A (2009):** Nail changes in alopecia areata: frequency and clinical presentation. Journal of the European Academy of Dermatology and Venereology, 23(2): 240–241.
31. **Brajac I, Tkalcic M, Dragojević D *et al.* (2007):** Roles of stress, stress perception and trait-anxiety in the onset and course of alopecia areata. The Journal of Dermatology, 30(12): 871–878.
32. **Madani S, Shapiro J (2005):** Alopecia areata update. Journal of the American Academy of Dermatology, 42(4): 549–570.
33. **Goh C, Tan K (2009):** Chronic autoimmune urticaria: where we stand?. Indian Journal of Dermatology, 54(3): 269–274.
34. **Otberg N (2011):** Systemic treatment for alopecia areata. Dermatologic Therapy, 24(3): 320–325.
35. **Alsantali A (2011):** Alopecia areata: a new treatment plan. Clinical, Cosmetic and Investigational Dermatology, 4: 107–115.