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THE PATTERN AND CLINICAL PROFILE OF ALOPECIA AREATA. PANORAMIC REVIEW: UPDATE AND ADVANCES ON ETIOPATHOGENESIS, ASSOCIATED FACTORS, DIAGNOSIS, COMPLICATIONS, MANAGEMENT AND PROGNOSIS IN TREATMENT 2023

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SUMMARY

Introduction: *Alopecia areata (AA) is a chronic disorder in which the immune system affects the hair follicles, nails, and occasionally, the retinal pigment epithelium. The characteristic manifestation of alopecia areata encompasses isolated, smooth, non-scarring surfaces of hair loss on the scalp or anywhere with hair growth.*
Objective: to detail the current information related to alopecia areata, etiology, epidemiology, pathophysiology, histopathology, manifestations, diagnosis, treatment and complications of the condition.
Methodology: *a total of 48 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 32 bibliographies were used because the other articles were not relevant for this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: alopecia areata, hair loss, hair follicles, hair loss, Janus kinase.*

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Results: *The lifetime risk of presenting alopecia areata is approximately 2%, it is the second most frequent non-scarring alopecia, after male and female pattern alopecia. So far no study has shown whether the prevalence of alopecia areata is different between ethnic groups. The first appearance of this alteration is more common between the third and fourth decades of life, however it can occur in any age group. Recent evidence suggests that the origin of the condition is autoimmune, with a significant genetic contribution. This alteration is related to medical and psychiatric comorbidities such as depression, anxiety and different autoimmune disorders.*

Conclusions: *Alopecia areata is an autoimmune condition that generates a sudden and uneven hair loss, affecting any area of the body. Recently, alopecia areata has been interpreted as an autoimmune disease with a genetic substrate. The hair follicles do not suffer permanent damage, which is positive because of the possibility of regrowth. It is of vital importance to know the etiology, epidemiology, pathophysiology, histopathology, manifestations, diagnosis and treatment of the condition. At the moment there is no cure for alopecia areata, however the use of some medications has contributed to the improvement of the symptomatology, there are multiple treatment options available. More studies are needed to treat this condition more adequately.*

KEY WORDS: *alopecia areata, hair follicles, hair loss, Janus kinase.*

INTRODUCTION

Alopecia areata (AA) is a chronic disorder in which the immune system affects hair follicles, nails and sometimes the pigment epithelium of the retina. This disorder occurs in about 2% of the general population and is due to the immune system mistakenly attacking the hair follicles, causing hair loss without permanently damaging the follicles. Several genetic and environmental factors support the pathogenesis of AA. The characteristic manifestation of alopecia areata encompasses isolated, smooth, unscarred surfaces of hair loss on the scalp or anywhere with hair growth. Occasionally some individuals affected with the condition experience spontaneous hair regrowth within a year, however, alopecia areata is a chronic recurrent condition. There are some management alternatives available, including corticosteroids, Janus kinase (JAK) inhibitors, immunotherapy and topical solutions, to control the spread and duration of hair loss. The first clinical description of alopecia areata is attributed to Celsius in 14-37 BC and the name alopecia areata is thanks to Sauvages. Later Hebra noted the incorrectness of the hypothesis of fungal etiology proposed by Willan and Gruby in 1843. Some time later, Von Baresprung originated the tropho-fungal theory, and Jacquet elaborated the dystrophic theory, considering infectious foci, especially dental, as the cause of the condition. Recently, alopecia areata has been interpreted as an autoimmune disease with a genetic substrate. This article gives an overview of the subject with emphasis on etiology, epidemiology, pathophysiology, histopathology, manifestations, diagnosis, treatment and complications of the condition(1-4).

METHODOLOGY

A total of 48 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 32 bibliographies were used because the information collected was not important enough to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: alopecia areata, hair loss, hair follicles, hair loss, Janus kinase.

The choice of bibliography exposes elements related to alopecia areata; in addition to this factor, etiology, epidemiology, pathophysiology, histopathology, manifestations, diagnosis, treatment and complications of the condition are presented.

DEVELOPMENT

Etiology

The hair cycle has 3 phases:

- Anagen: active hair growth is generated.
- Catagen: keratinization of the proximal end of the hair shaft occurs, then the hair follicle detaches and the remaining proximal end undergoes apoptosis.
- Telogen: represents the interval between the regression of the old follicle and the beginning of the next anagen phase.

In the anagen phase there are 6 stages of hair growth, with stage VI representing a fully formed anagen follicle, alopecia areata is an autoimmune disorder that alters this process. However, in individuals affected with alopecia areata, the hair follicles stop in stages III or IV, returning early to the catagen or telogen phase, resulting in sudden hair loss and a deficiency in hair growth(2).

Epidemiology

The lifetime risk of presenting alopecia areata is around 2%, showing a prevalence close to 1 in 1000. The data does not dictate a sexual predilection, however it shows a higher incidence among Asians, blacks and Hispanic individuals. Alopecia areata is the second most common non-scarring alopecia, the first being male and female pattern alopecia. Most studies show no significant differences in duration, age of onset, type of alopecia areata by sex or ethnicity. The most common is to present the first appearance between the third and fourth decades of life, however it can appear at any age. The earlier age of onset is associated with a higher risk of developing extensive disease later in life. This alteration is related to several medical and psychiatric comorbidities such as depression, anxiety, as well as multiple autoimmune disorders(5-7).

Alopecia areata can occur at all ages, however, its incidence increases steadily with age, the average age of onset is 32 years in men and 36 years in women(2,8).

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Pathophysiology

Some critical body organs such as the testes, the central nervous system, the eyes, the fetus and the placenta, present immunological privilege, which means that they have the capacity to withstand exposure to antigens without generating an inflammatory immune response. The loss of immune privilege inside the hair follicles and the consequent immune dysregulation play an important role in the development of alopecia areata(5,6).

It is currently thought that the origin of the condition is autoimmune, with a significant genetic contribution, which in turn depends on some unknown environmental factors. Some of the triggers include vaccinations, viral infections, physical or emotional stress and medications. These triggers inhibit the manufacture of two anti-inflammatory cytokines, alpha-melanocyte stimulating hormone (α-MSH) and transforming growth factor beta (TGF-β). There is also increased expression of major histocompatibility complex class I (MHC-I) polypeptide-related sequence A (MICA) in hair follicles. Then, natural killer cells are activated, causing secretion of interleukin (IL)-15 and interferon gamma (IFN-γ)(1,2).

IFN-γ stimulates the expression of MHC-I proteins in hair follicle cells, revealing previously hidden antigens to T cells. Uniquely, IL-15 inhibits regulatory T cells. IFN-γ and IL-15 activate immune target cells via the JAK signal transducer and activator of transcription signaling pathway (JAK-STAT). Consequently, the inflammatory cells go to the matrix epithelium of the hair follicle undergoing early cortical differentiation (anagen hair follicles), bringing them prematurely into the catagen or telogen phase(2,6).

Currently, associations between alopecia areata and copy number variations (CNV) were found through genome-wide scans(9-11).

Histopathology

Histopathologic evidence observable at the surface where acute active hair loss occurs shows a unique "bee swarm pattern" characterized by dense lymphocytic infiltrates around the bulbar region of anagen hair follicles. The lymphocytic infiltrate consists of CD8+ T cells within the follicular epithelium and CD4+ T cells around the hair follicles. Biopsies from sites with chronic alopecia involvement show follicular miniaturization(1,2,12).

Manifestations

Initially, alopecia areata is diagnosed through the identification of waxing and waning focal alopecia anywhere on the body, most commonly on the scalp. It usually manifests as isolated patches of hair loss on the scalp that form within a few weeks. However, the disorder can affect the eyelashes, beard, eyebrows and extremities. Exclamation-sign hairs, characterized by a proximal end narrower than the distal end, may be seen at the periphery of lesions in active disease. A low portion of affected individuals may progress to complete scalp hair loss, which is called alopecia areata totalis. On the other hand, there are patients who go on to present total hair loss over the entire body, which is called alopecia universalis.

There are multiple types of alopecia areata, among which we have:

- Ophiasis: hair loss in the occipital region, being a band-like hair loss along the circumference of the head, particularly along the margin of the temporal and occipital bones.
- Sisyphus pattern (ofiasis inversus): hair loss on the frontal, temporal and parietal scalp, respecting the occipital region, being an extensive alopecia except around the periphery of the scalp.
- Diffuse: rapidly progressive and diffuse hair loss followed by regrowth in a few months.
- Patchy alopecia areata: one, several separate patches or clusters of hair loss.
- Total alopecia: complete or almost complete loss of hair on the scalp.
- Universal alopecia: complete or almost complete loss of hair on all hair-bearing surfaces of the body.
- Alopecia incognita: diffuse complete hair loss with positive tensile test, short, miniaturized hairs that grow back, yellow spots, without nail involvement.
- Marie Antoinette syndrome (sudden graying) is an acute episode of diffuse alopecia with very sudden "overnight" graying with preferential loss of pigmented hair.

About 10% to 15% of affected individuals present nail involvement, with fine pitting of the nails, red spots on the lunulae, onycholysis, trachyonychia, onychorrhexis and onychomadesis. Individuals with alopecia areata are also at high risk for conditions such as retinal vein occlusion, retinopathy and retinal detachment(1,2,5,6,13).

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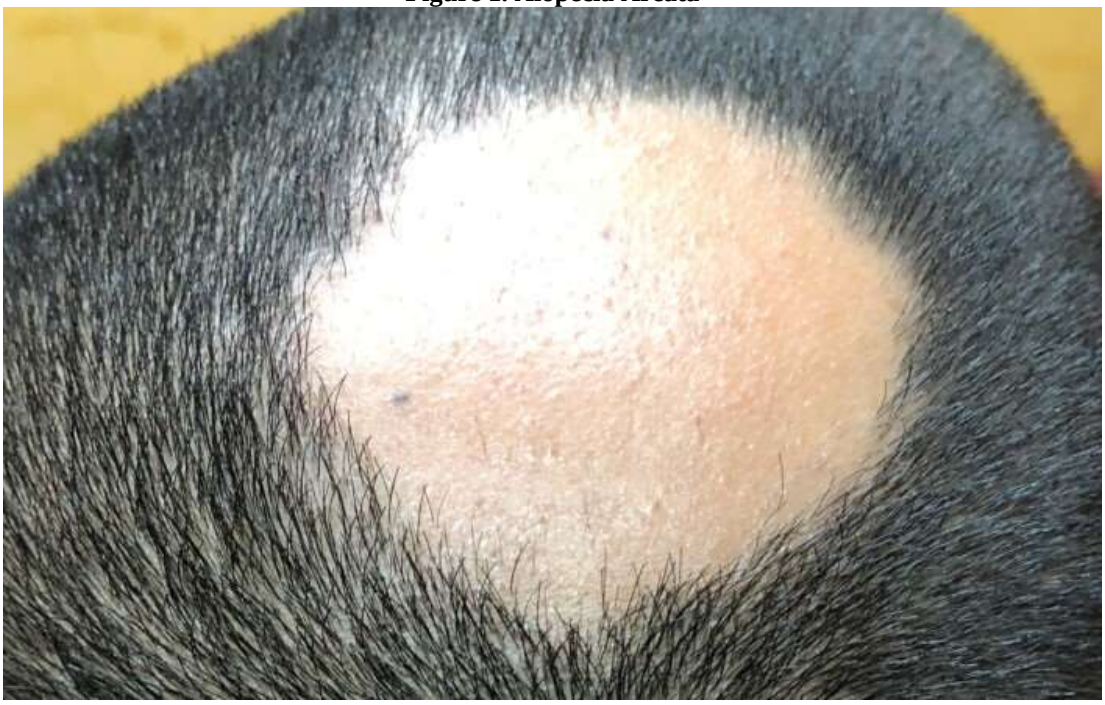
Figure 1. Alopecia Areata



Source: Lepe K, Syed HA, Zito PM. Alopecia Areata. In: StatPearls [Internet](2).

Diagnosis

It is primarily clinical and depends on the medical history and physical examination of the affected individual. Clinical suspicion should increase when a disorder presents with a rapid development of individual patches of alopecia on the skin, usually accompanied by little or no erythema. Dermoscopy is often a useful tool in complementary diagnosis(14,15).

Early regrowth is indicated by yellow spots, black spots, hairs with exclamation marks, broken hairs and short vellus hairs, which are key features at the time of diagnosis. A skin biopsy from the periphery of a patch of active hair loss becomes beneficial when the diagnosis is still uncertain. Although alopecia areata is related to several autoimmune diseases, the evidence does not currently support routine screening unless the individual's clinical presentation suggests the possibility of alopecia areata(6,16).

Treatment and Prognosis

In one year, about half of the individuals experienced spontaneous hair regrowth without treatment. For those who opt for treatment, intralesional and topical corticosteroids are generally used as first-line therapy for most cases of patchy alopecia areata. There are studies in which triamcinolone acetonide at concentrations of 5 to 10 mg/ml, administered every 4 to 6 weeks on the scalp, promotes localized growth 60% to 67% of the time. Triamcinolone concentrations of 2.5 to 5 mg/ml are commonly used for the beard and eyebrows. New hair growth is usually seen within 6 to 8 weeks. A clinical study compared multiple concentrations of intralesional triamcinolone acetonide (2.5 mg/ml, 5 mg/ml and 10 mg/ml) for the management of alopecia areata of the scalp showing similar hair regrowth rates regardless of the concentration applied. However, it is important to highlight that the risk of cutaneous atrophy was significantly higher using higher concentrations of triamcinolone (10 mg/ml). The use of intralesional betamethasone needs more studies to analyze its efficacy. Some of the adverse effects that corticosteroids may present are localized skin atrophy, pain and depigmentation. Using intralesional corticosteroids on the face can result in noticeable hypopigmentation in individuals with darkly pigmented skin. Although localized skin atrophy usually resolves within a few months, relapses are common after discontinuation of treatment(2,17-20).

Betamethasone dipropionate 0.05% is a potent topical glucocorticoid used in the treatment of alopecia areata. Topical corticosteroids are usually reserved for children and individuals who cannot tolerate multiple injections. Afflicted individuals should be placed on betamethasone daily for 3 months, if there is no improvement in the condition it is recommended to discontinue the medication. On the other hand, when there is notable progress, it is suggested to affected individuals to maintain the betamethasone while they proportionally decrease the dose(2,6).

Several therapies have been used for the management of children and adolescents with alopecia areata, however the efficacy is variable. Topical corticosteroids present more evidence with the treatment of the condition in children, followed by contact

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immunotherapy. At the moment more scientific evidence is required to better guide the management of pediatric AA(21).

Individuals with extensive, classically defined disease, i.e. those with more than 50% scalp hair loss, may consider using topical immunotherapy or oral baricitinib to avoid numerous injections associated with intralesional corticosteroids. Retrospective studies show superior efficacy of topical immunotherapy versus intralesional corticosteroids in patients with patchy hair loss greater than 50 cm^2.

A potent contact allergen, such as diphenylcyclopropenone (DPCP) or squaric acid dibutyl ester (SADBE), can be placed on the scalp weekly to encourage hair growth. Hair growth can then be seen around 3 months after the start of treatment, however it is important to note that severe dermatitis can occur as an adverse effect. A current meta-analysis examining contact immunotherapy for alopecia areata showed that 74.6% of those with patchy alopecia showed hair regrowth, compared to 54.4% of individuals with alopecia totalis and alopecia universalis. The recurrence rates were 38.2% in individuals who had maintenance treatment, on the other hand, 49% in those who did not have maintenance treatment(2,19,22).

A selective and reversible inhibitor of JAK1 and JAK2, called oral Baricitinib, treats alopecia areata by eliminating T-lymphocyte activation. Individuals generally need continuous therapy to continue to have the benefits achieved. There is a warning for JAK inhibitors because of the risk of serious infections, mortality, major adverse cardiovascular events and thrombosis. Adjunctive therapies that have shown some efficacy include platelet-rich plasma, anthralin, topical or oral minoxidil, excimer laser and PUVA. Systemic glucocorticoids can generate hair growth, but are not frequently used because of adverse effects; however, individuals with rapid and extensive hair loss may improve with oral glucocorticoids. Some systemic therapies, such as azathioprine, methotrexate, etanercept and cyclosporine, have shown multiple clinical responses. Some of the treatments currently under investigation are hydroxychloroquine, recombinant IL-2 and simvastatin with ezetimibe(6,23-29).

At the moment, topical therapy for eyelashes is not effective, improvement can be achieved with systemic therapy and the use of false eyelashes is common. Other cosmetic alternatives are tattooed eyebrows, hairpieces, wigs and head shaving. The condition also causes other problems such as anguish, anxiety and depression, which sometimes requires a psychologist or psychiatrist. A family history of alopecia areata, atopy, nail dystrophy, or concomitant autoimmune disease may be indicative of a poor prognosis(1,2,6,30).

Complications

Among the probable complications of alopecia areata are the following symptoms:

- Unpredictable pattern, texture, and rate of hair growth.
- Recurrence.
- Permanent hair loss.
- Nail abnormalities.
- Increased risk of developing thyroid disease, lupus erythematosus, atopic dermatitis, vitiligo and psoriasis.
- Depression and anxiety.
- Sunburn and skin damage.
- Skin atrophy, hypopigmentation, dermatitis, infections, malignant neoplasms, thrombosis due to adverse reaction to medication.

In patients with alopecia areata there is evidence of a 3 times higher risk of triggering retinal diseases(2,31,32).

CONCLUSIONS

Alopecia areata is an autoimmune condition that causes sudden and uneven hair loss, affecting any area of the body. Recently, alopecia areata has been interpreted as an autoimmune disease with a genetic substrate. The hair follicles do not suffer permanent damage, which is positive because of the possibility of regrowth. It is of vital importance to know the etiology, epidemiology, pathophysiology, histopathology, manifestations, diagnosis and treatment of the condition. At the moment there is no cure for alopecia areata, however the use of some medications has contributed to the improvement of the symptomatology, there are multiple treatment options available. More studies are required to treat this condition more adequately.

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