# ALOPECIA AREATA - ASSOCIATIONS WITH ATOPY AND AUTOIMMUNE DISEASES

# ALOPECIA AREATA – ASOCIEREA CU ATOPIE ȘI AFECȚIUNI AUTOIMUNE

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## Abstract

Alopecia areata (AA) is a common condition presenting in dermatological practice. Evidence suggest that T cell autoimmune reactions along with genetic predisposition and environmental triggers play important roles in the development of AA. A multitude of autoimmune diseases and also atopic disease have been incriminated to be more frequent in patients with AA. New evidences based on large scale studies support and define these associations and these findings can improve the clinicians strategy when dealing with AA.

**Keywords:**

alopecia areata, atopy, autoimmune diseases

## Rezumat

Alopecia areata (AA) este o afecțiune comună în practica dermatologică. Dovezile din literatură sugerează că mecanisme autoimune mediate prin limfocite T împreună cu predispoziția genetică și factorii de mediu joacă roluri importante in dezvoltarea AA. O multitudine de afecțiuni autoimune dar și atopia au fost incriminate ca fiind frecvente printre cei cu AA. Noi dovezi bazate pe studii pe scară largă susțin si definesc aceste asocieri, iar aceste noi informații pot inbunătăți strategia clinicianului în managementul AA.

**Cuvinte-cheie:**

alopecia areata, atopie, afecțiuni autoimune

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## INTRODUCTION

Alopecia areata (AA) is a T cell mediated disease that targets anagen-stage hair follicles. [1,2] Commonly presenting as sudden-onset, nonscarring hair loss and is often psyhologically devastating with huge cosmetic impacts and therapeutic challenges. [1, 2, 3]

It affects both sexes equally, can occur early in life or present in adulthood, and has lifetime risk estimated to be 1,7% for the general population with an incidence rate of 20,2 per 100.000 person-years. [3, 5] AA is reported to account for approximately 2% of new visits to outpatient dermatology clinics in the USA and the UK. [1]

Although environmental factors may trigger the initiation of the disease in genetically predisposed individuals, the exact cause is still unknown. [4, 5] Alopecia areata is considered an autoimmune disease with undetermined pathogenesis. Studies suggest that atopy and autoimmune diseases are risk factors for AA. It is important to be aware of the implications and physicians caring for patients with AA should consider screening for comorbid conditions.

## EVIDENCES

Important studies that link the association of AA with atopy and autoimmune diseases have been published lately. They support the previous data, even though most of the studies are either limited to small population or by self-reported conditions.

We used PubMed to find the most significant studies conducted in the last five years.

A history of atopy and autoimmune disease was associated with a statistically significant risk of AA in a study conducted on 2613 self-registered sporadic cases of AA. [20] The results were consistent for both the severe subtype of AA (ie, alopecia totalis and alopecia universalis) and the localized subtype (ie, AA persistent). The prevalence of atopy among patients with AA in this study was 39%, compared with 60,7% and 46% reported for AA by Tan et. al. and Goh et. al., respectively. [20, 6, 7] The prevalence of having autoimmune disease was 16%, compared with the 12% to 25% observed in previous studies. [20, 6, 7]

To clarify the role of atopic and autoimmune disease in AA, therefore better understanding its pathogenesis, a total of 4334 patients with AA were included in one retrospective study conducted from 1996 to 2008. [5] Among patients with AA there were significant associations with vitiligo, lupus erythematosus, psoriasis, atopic dermatitis, autoimmune thyroid disease, and alergic rhinitis. Different ages at onset resulted in disparate comorbidities. Most atopic and autoimmune diseases were observed at onset ages of 21-60 years. Moreover, patients with AA had higher risk for more coexisting diseases than control subjects. Numerous studies have reported that AA is associated with atopic diseases. Among them atopic dermatitis showed more significant association with AA than atopic rhinitis and asthma in this study. [20, 5]

In 2013 a retrospective cross-sectional study that assesed the comorbidity profiles among patients with AA and the importance of onset age was published. [8] Common comorbid conditions included autoimmune diagnoses (thyroid disease in 14,6%, diabetes mellitus in 11,1%, inflammatory bowel disease in 2%, systemic lupus erythematosus in 4,3%, rheumatoid arthritis in 3,9%, and psoriasis and psoriatic arthritis in 6,3%), atopy (allergic rhinitis, asthma, and/or eczema in 38,2% and contact dermatitis and other eczema in 35,9%), and mental health problems (depression or anxiety in 25,5%). This study also found high prevalences of hyperlipidemia (24,5%), hypertension (21,9%), and gastroesophageal reflux disease (17,3%). [8]

A sistematic review and meta-analysis to compare the prevalence of atopic dermatitis between patients with either vitiligo or AA and those without these disorders was published in December 2014. In total, 16 studies of vitiligo and 17 studies of AA were included. In the pooled analysis of the studies that included control patients without vitiligo and control patients without AA, patients with vitiligo had significantly higher odds of atopic dermatitis than did control patients without these disorders. Pooled analysis of four studies found higher odds of atopic dermatitis in patients with alopecia totalis or alopecia universalis compared with those with patchy alopecia. [9]

Van der Spek et. al. reported that juvenile AA was more severe and had a less favourable prognosis than the maturity onset disease. [10] In one study the frequencies of autoimmune and atopic diseases were not different between adult and paediatric patients and the control group. Furthermore, the investigators did not find a statistically significance between disease severity and personal and family history of autoimmune disease in the two groups. [4]

## DISCUSSIONS

Currently, the mechanisms explaining an association among atopy, autoimmunity, and AA are not fully understood. Previous studies have provided evidence that a history of atopy and autoimmune diseases are also risk factors for AA. [4, 5, 6, 7, 8, 9, 20]

AA is considered to be an autoimmune disease caused by CD41 and CD81 T cells invading immune-privileged anagen-stage hair follicles causing a loss of tolerance. [5. 11, 20] Both T helper 1 (Th1) and T helper 2 (Th2) cytokine responses are involved with animal models of AA, which could explain the association of AA with both antibody mediated (systemic lupus erythematosus and autoimmune trombocytopenic purpura) and T cell mediated autoimmune diseases (Hashimotto thyroiditis and vitiligo). [2, 5, 12, 13, 20] The ability to transfer AA by bone-marrow transplantation in an unaffected HLA matched healthy individual was demonstrated and supports the fact that T cells mediate AA. [2,13] More than that, major histocompatibility genes on chromosome 6p21 encoding HLA antigenes have been shown to be a major determining loci for autoimmune diseases including AA. [14, 20] The association of AA with autoimmune disease is very strong and is suported by the latest populational studies. [4, 5, 7, 8, 9, 12, 15, 20] One of the four subtypes of AA in the Ikeda classification is the atopic one (10%). [21] Immune cells attack the skin in both AA and atopic dermatitis. [1,5,11, 16,17,18,20] AA and atopy share a Th2 cytokine pattern and increased levels of IgE antibodies, mast cells, and eosinophils. [5, 20] Even though atopic dermatitis

and AA are both common inflammatory skin diseases, they involve different mechanisms: atopic dermatitis as predominantly Th 2 - mediated and AA as predominantly Th 1 - mediated. [16, 17, 18] There has been recent evidence, however, that suggest that these immune mechanisms may not be so clear cut in either disease, especially in their chronic forms. [7, 11, 16] There is a Th2 (interleukin (IL) 4) response in localized AA versus a Th1 (interferon (IFN) - gamma) response in generalized AA. Similarly, there is a Th2 response in acute phase of atopic dermatitis (IL 4) whereas the important role of Th1 response (IFN-gamma) is only seen in later stages of atopic dermatitis. Thus, this similar biphasic pattern of Th response in AA and AD may also account for the increased risk of atopic dermatitis in patients with AA. [11, 16, 17, 20] In addition Th2 cytokines (IL4 and IL13) also influence epidermal barrier function by downregulating the filaggrin gene expresion, encoding a protein of the keratin cytoskeleton. [17, 20] The upregulation of RANTES (regulated upon activation, normal T cell expressed and secreted), a chemoatractant for eosinophils, is increased in both AA and atopic dermatitis. [11, 16, 17, 20]

Since 1963 Muller SA and Winkelmann RK found that a personal history of asthma and/or atopic dermatitis in 18% of children and 9% of the adults in their series. [19] Atopic disease was associated with all forms of AA. [5, 8, 9, 20] Most of the findings show that atopic dermatitis is more frequent than asthma or allergic rhinitis in patients. [5,20] In addition, the association seems to be higher for the more severe forms of AA, alopecia totalis and alopecia universalis respectively. [9] The conglomeration of more than one autoimmune disorder is common, even though there are studies that showed no evidence that the history of more than one atopic or autoimmune disease increased the risk of AA. [5] A multitude of immune reactions are involved in AA, therefore it seems that the risk for autoimmune or atopic diseases increases with the number of these diseases in patients with AA. A cumulative effect of different kinds of immune responses might exist. [20]

## CONCLUSIONS

1. AA is related to various atopic and autoimmune diseases. The clinician must be aware of these associations and efficiently investigate specific comorbidities.

2. Further studies are necessary to elucidate the underlying mechanisms and the common pathogenic pathways involved in atopy, autoimmune diseases, and AA.

3. Maybe a new classification of AA is needed allowing greater importance to the specific forms of AA that can be included in the atopic and/ or autoimmune status.



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