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Etiology and Pathophysiology of Alopecia Areata: A Narrative Review

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Abstract

Alopecia areata is a common, non-scarring, immune-mediated hair loss disorder arising from the breakdown of the hair follicle's immune-privileged state. This paper presents a narrative review of its etiology, integrating genetic susceptibility, immune privilege collapse, cytokine-driven autoimmune injury, environmental and psychological triggers, and the emerging role of the cutaneous and gut microbiome. We conclude that Alopecia areata etiology is best conceptualized as a threshold model in which genetically primed hair follicles undergo immune privilege collapse following one or more environmental, infectious, oxidative, or psychosocial triggers, and that trichological assessment should systematically screen for each of these domains.

Keywords: alopecia areata; hair follicle immune privilege; autoimmune hair loss

1. Introduction

Alopecia areata is a chronic, relapsing, organ-specific autoimmune disorder characterized by non-scarring patchy or diffuse hair loss on the scalp and, less commonly, other hair-bearing sites. Lifetime prevalence estimates range up to approximately 2% of the population, with onset possible at any age but most frequently before the fourth decade of life. From a trichological standpoint, Alopecia areata is of particular interest because it sits at the intersection of hair follicle biology, immunology, and psychosocial health — a triad that a practicing trichologist must evaluate holistically rather than treat as a purely dermatological curiosity.

This paper synthesizes current understanding of Alopecia areata etiology with the aim of providing clinicians with an etiology-first framework for assessment and referral.

2. Etiology and Pathogenesis

2.1 Collapse of Hair Follicle Immune Privilege

The anagen hair bulb is an immune-privileged site, normally shielded from immune surveillance by low expression of MHC class I and II molecules, local immunosuppressive signalling (including TGF-β, IL-10, and α-melanocyte-stimulating hormone), and an absence of resident antigen-presenting activity around the lower follicle. The central pathogenic event in Alopecia areata is the collapse of this privilege: MHC class I/II molecules become aberrantly upregulated, follicular autoantigens are exposed, and autoreactive CD8+NKG2D+ T cells — recruited and sustained by interferon-γ (IFN-γ) and interleukin-15 (IL-15) signalling through the JAK–STAT pathway — infiltrate the peribulbar region and arrest the hair cycle prematurely, forcing anagen follicles into catagen/telogen.

2.2 Genetic Susceptibility

Alopecia areata shows clear familial clustering and concordance in twin studies, consistent with a polygenic predisposition. Genome-wide association studies have implicated loci shared with other autoimmune diseases, including polymorphisms in PTPN22, CTLA4, IL2RA, and the FAS/FASL apoptotic pathway, alongside HLA class II associations. Gene-expression profiling of lesional scalp consistently shows an interferon-γ response signature (e.g., upregulation of CXCL9, CXCL10, and CXCL11) together with downregulation of hair keratin (KRT) and keratin-associated protein (KRTAP) genes, linking genetic risk directly to the follicular structural proteins targeted by the autoimmune attack.

2.3 Environmental, Infectious, and Physical Triggers

Alopecia areata onset and relapse are frequently reported in temporal association with viral infections (including influenza), which are thought to provoke a surge in type I/II interferons capable of tipping a genetically primed follicle into immune privilege collapse. Physical trauma to the scalp, vaccination, and other acute immunologic stimuli have also been reported as possible triggers, although causal evidence remains largely observational.

2.4 Psychological and Neuroendocrine Stress

A bidirectional relationship exists between Alopecia areata and psychological stress. Acute or chronic stress is a commonly reported antecedent of disease onset and flares, and is proposed to act via neuroendocrine mediators (e.g., substance P, corticotropin-releasing hormone) that can locally disrupt the perifollicular immunosuppressive milieu, lowering the threshold for immune privilege collapse. Conversely, the visible and often stigmatizing nature of Alopecia areata hair loss frequently produces secondary anxiety and depressive symptomatology, creating a feedback loop that a trichologist should proactively screen for and, where appropriate, address through referral to mental health support.

2.5 Oxidative Stress

An imbalance between reactive oxygen species and antioxidant defenses has been documented in Alopecia areata patients and is hypothesized to contribute to, or accelerate, the collapse of follicular immune privilege, potentially by upregulating stress-response and danger-associated molecular signalling within the hair bulb. This has generated interest in antioxidant strategies as adjunctive, though not primary, management.

2.6 Cutaneous and Gut Microbiome

Emerging evidence implicates alterations in scalp and gut microbial communities as a modulating factor in Alopecia areata, analogous to microbiome associations described in other autoimmune diseases. Dysbiosis is proposed to influence local and systemic immune tone, though the literature in this domain remains preliminary and the microbiome should currently be regarded as a contributing modifier rather than a primary etiological driver.

2.7 Integrative (Threshold) Model of Etiology

Taken together, the literature supports a threshold model: a genetically susceptible hair follicle maintains immune privilege until a sufficient combination of triggers — infectious, physical, oxidative, or psychological — accumulates to precipitate MHC upregulation and IFN-γ/IL-15/JAK-STAT-driven autoimmune attack. This model explains the heterogeneity of Alopecia areata presentations (patchy, ophiasis, totalis, universalis) and the variability in which a genetic autoimmune background, a recent viral illness, and psychosocial stress plausibly converged.

3. Conclusion

Alopecia areata is best understood not as a single-cause disease but as the clinical endpoint of a threshold interaction between genetic susceptibility and one or more environmental, infectious, oxidative, or psychological triggers acting on an immune-privileged hair follicle. A trichological assessment that systematically evaluates each of these domains — family and genetic history, recent infectious or physical triggers, psychosocial stress, and trichoscopic markers of disease activity — provides a more complete etiological picture and supports more rational referral for mechanism-targeted therapy where indicated.

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