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Pathogenetic Mechanisms of Alopecia Associated with Chronic Stress

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Abstract Alopecia is a common dermatological condition with significant psychosocial impact. Increasing evidence suggests that stress plays a key role in the pathogenesis of alopecia, including androgenetic alopecia, alopecia areata, and telogen effluvium, through neuroendocrine and immune mechanisms. This study analyzes the influence of psychogenic factors, hormonal and immune dysregulation, and psychosomatic disturbances in patients with alopecia, as well as their impact on quality of life. Psychometric tools such as the Dermatology Life Quality Index (DLQI), Skindex-29, and the Hospital Anxiety and Depression Scale (HADS) were used to assess psychological status. Stress is associated with increased inflammatory cytokines, elevated cortisol levels, disruption of the hair growth cycle, and follicular alterations. Psychological comorbidities, including anxiety and depression, are highly prevalent and significantly reduce quality of life. Alopecia should be considered a psychoneuroendocrine disorder requiring a multidisciplinary approach. Integration of psychological assessment into clinical practice may improve treatment outcomes.

Keywords Alopecia, Androgenetic alopecia, Alopecia areata, Telogen effluvium, Stress, Psychosomatic disorders, Neuroendocrine regulation, Cytokines, Cortisol, Nerve growth factor, Quality of life, HADS, DLQI, Skindex-29

1. Introduction

Alopecia has increasingly become a significant aesthetic and medical concern in recent years, which is associated with environmental deterioration, poor water quality, and changes in dietary patterns. Dermatological conditions such as atopic dermatitis and psoriasis play a substantial role in the development of alopecia, with their prevalence rising markedly among both adults and children. It has been reported that approximately 30–40% of patients with alopecia are concurrently diagnosed with atopic dermatitis [1].

In addition, alterations in the skin microbiome have been identified as an important contributing factor in the pathogenesis of alopecia [2]. However, particular attention in recent years has been directed toward psychological stress as a key pathogenetic trigger of hair loss.

As of 2019, approximately 18.4 million cases of alopecia areata (AA) have been reported worldwide. Given the significant cosmetic and social role of human hair, partial or complete hair loss can lead to considerable psychological distress. Although alopecia is generally considered a benign condition, it can have a profound impact on patients' psycho -emotional well-being [4,6].

Hair plays a particularly important role in maintaining psychological balance in women compared to men. Concepts such as femininity, sexuality, attractiveness, and individuality are symbolically associated with the condition of women's hair. Therefore, hair loss can significantly affect not only physical appearance but also self-esteem and overall psychological status of female patients [6]. Diffuse telogen effluvium is the most common type of hair loss [1]. Among the wide range of triggering factors, severe emotional stress plays a key role in the development of diffuse telogen hair loss. Traditionally, psycho-emotional disturbances were often considered a consequence rather than a cause of the disease.

However, exposure to psychotraumatic factors contributes to the onset or exacerbation of cutaneous manifestations in a significant proportion of patients with seborrheic hair thinning and in up to 87% of patients with alopecia areata [4,12].

Psychosomatic pathological processes are characterized by several distinct clinical and pathogenetic features. The following clinical characteristics have been identified in patients with alopecia: pronounced psychovegetative disorders, persistent exposure to chronic stress, gradual chronification of the dermatological process initiated under stress conditions, a tendency toward a chronic relapsing course, and long-term persistence and progression of the disease. These features often preclude spontaneous remission and limit the effectiveness of conventional therapeutic approaches [3,5,7].

From a pathogenetic perspective, psychosomatic disorders are associated with constitutional predisposition, involvement of psychovegetative dysfunction in the development of

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multiple pathological mechanisms, and the formation of a pathological "vicious circle," in which existing disturbances reinforce and perpetuate disease progression [4–6].

2. Immunoregulatory Indices in Stress-Induced Hair Loss

Stress is a well-established factor contributing to the exacerbation of dermatological diseases and plays a crucial role in the development of immune dysregulation, leading to inflammatory processes in the hair follicle microenvironment. Both acute and chronic stress activate cytokine signaling pathways, including interleukins (IL-1, IL-4, IL-6, IL-8, IL-13), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and others [4].

Pro-inflammatory cytokine pathways and their associated secondary messengers represent promising therapeutic targets for the development of anti-alopecia treatments. Concurrently, increased levels of corticosteroids are observed in the skin and in the perifollicular area. This contributes to the formation of a pathological "vicious cycle," in which corticosteroids themselves promote immune-mediated reactions in the hair follicle environment [4].

In addition, stress induces upregulation of receptors for hypothalamic and pituitary signaling peptides in skin cells, particularly keratinocytes and fibroblasts. There is also an increased expression of receptors for key neurotransmitters, including adrenaline, noradrenaline, dopamine, histamine, and acetylcholine on keratinocytes, which further sustains and amplifies stress-related signaling pathways [5].

The detrimental effects of stress on the skin also include disruption of keratinocyte structural proteins, loss of basement membrane components, and degradation of collagen. Cortisol levels serve as an important biomarker of hypothalamic–pituitary axis activation in response to stress; notably, chronic stress is associated with a significant increase in cortisol concentration in hair [13].

Under normal physiological conditions, stress is accompanied by the release of corticotropin-releasing factor (CRF), triggering a cascade of reactions that ultimately result in the secretion of glucocorticoids. Through a negative feedback mechanism, glucocorticoids subsequently inhibit CRF secretion, thereby restoring the system to its baseline state [22].

However, psychotraumatic events, chronic stress, and genetically determined dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis can disrupt this feedback mechanism, leading to prolonged persistence of glucocorticoids [12,13].

A number of studies have demonstrated the significant impact of stress-related hormones, including cortisol, prolactin, and adrenocorticotropic hormone (ACTH), on hair physiology and overall organismal homeostasis [13,22].

Stress can enhance the secretion of pro-inflammatory cytokines, including interferon-gamma (IFN-γ), leading to inflammatory responses that ultimately result in apoptosis, cellular senescence, and disruption of the hair growth cycle, with premature transition to the catagen phase [4,23].

Studies have shown that elevated cortisol levels are associated with an approximately 40% increase in the degradation rate of key proteoglycans, such as decorin and versican. This process is accompanied by a decline in the activity of selective proteoglycans within the dermal papilla, which in turn contributes to increased hair shedding, restricted hair growth, and deterioration of hair quality [13,14].

Furthermore, the production of proteoglycans by fibroblasts is reduced under stress conditions. As a result, the hair follicle loses essential structural and regulatory components, leading to impaired function. This condition, referred to as follicular hypoglycania, progresses to proteoglycan-associated follicular atrophy and miniaturization of hair follicles [13,14].

It is evident that the anagen phase represents a particularly fragile and highly stress-sensitive stage of the hair cycle [30].

3. Hormonal Dysregulation in Stress-Induced Hair Loss

The analysis of hormonal status is of critical importance in understanding stress-induced hair loss. Overt, laboratory-confirmed hyperandrogenemia is observed in only approximately one in five female patients. However, the remaining patients typically exhibit hormonal alterations consistent with so-called functional hyperandrogenism, characterized by elevated levels of luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), and leptin, accompanied by reduced concentrations of sex hormone-binding globulin (SHBG) [15,31].

In women, androgenetic alopecia (AGA), particularly in the absence of pronounced endocrine pathology, should be considered as a component of metabolic syndrome. This perspective provides a basis for further investigation into the role of psycho-emotional stress, which is known to exacerbate insulin resistance and dyslipidemia [31].

It has been established that androgenetic alopecia (AGA) in women is associated with significantly higher levels of anxiety (standardized mean difference [SMD] = −0.50), social anxiety (SMD = −0.50), depression (SMD = −0.38), and perceived stress (SMD = −1.09) compared to control groups [6,24].

Gender-specific features of pathogenesis have also been identified, including increased aromatase activity and lower expression of 5α-reductase type II in women. Furthermore, chronic psychological stress has been shown to modulate the levels of neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), and to significantly reduce the effectiveness of standard therapeutic approaches [10,11].

Approximately 45% of female patients with AGA exhibit a type D personality profile, which is associated with maladaptive coping strategies. These findings substantiate

the need for integrating psychological assessment into routine clinical practice [9,24].

4. Psychological Factors in Alopecia Areata

The influence of psychological factors on the onset, progression, and therapeutic outcomes of alopecia areata (AA) has been well documented [12,27]. Acute emotional stress may act as a triggering factor for AA, potentially through activation of overexpressed corticotropin-releasing hormone receptor type 2 (CRH-R2) in the perifollicular region, leading to pronounced local inflammation [23].

In addition, stress has been shown to induce the release of substance P from peripheral nerve endings. Increased expression of substance P has been observed in nerve fibers surrounding hair follicles in patients with AA. Moreover, the enzyme neutral endopeptidase, responsible for the degradation of substance P, is also highly expressed in affected hair follicles during both acute progressive and chronic stable phases of the disease [7,23].

Failure to adequately address psychological stressors may result in the formation of a pathological "vicious cycle" between stress and disease activity, negatively affecting the clinical course of alopecia and reducing the effectiveness of therapeutic interventions. This situation may be further aggravated by unrealistically high patient expectations regarding treatment outcomes and duration. Persistent anxiety and uncertainty can lead to early dissatisfaction with therapy.

Therefore, assessment of psychological status is essential for improving quality of life and enhancing psychosocial adaptation in patients with alopecia.

5. Therapeutic Perspectives and Stress-Related Mechanisms in Hair Loss

Plant-derived adaptogens have been shown to contribute to the restoration of the skin barrier and maintenance of skin homeostasis, reduce oxidative stress, and improve intercellular interactions [8]. Of particular interest is ectoine, an amino acid derivative obtained from halophilic bacteria, which has demonstrated protective effects against the inhibitory action of cortisol on the expression of key functional skin proteins, including involucrin, loricrin, laminin-5, and claudin-1. Additionally, ectoine mitigates the negative impact of stress on collagen and hyaluronic acid synthesis and indirectly reduces the levels of endogenous glucocorticoids.

Previous studies have reported that elevated cortisol levels are associated with an approximately 40% increase in the degradation rate of key proteoglycans, such as decorin and versican. This is accompanied by a decline in the activity of selective proteoglycans within the dermal papilla, resulting in increased hair shedding, impaired hair growth, and deterioration of hair quality. Furthermore, stress conditions lead to decreased production of proteoglycans by fibroblasts.

Loss of proteoglycans disrupts normal follicular function, leading to a condition referred to as follicular hypoglycania, which subsequently progresses to proteoglycan-associated follicular atrophy and miniaturization of hair follicles [13,14]. The anagen phase is particularly vulnerable, representing a highly sensitive stage of the hair cycle that is easily disrupted by external and internal stressors.

Thus, stress exerts a detrimental effect on the finely regulated mechanisms of hair cycle dynamics and may act as a trigger for the onset or exacerbation of a wide range of trichological disorders, including alopecia areata, androgenetic alopecia, telogen effluvium, seborrheic dermatitis, psoriasis of the scalp, and cicatricial alopecias [4,10,13,14].

6. Conclusions

Current evidence supports the consideration of androgenetic alopecia (AGA) in women as a psychoneuroendocrine disorder requiring a multidisciplinary approach involving dermatologists, endocrinologists, and clinical psychologists. The development of standardized protocols for psychological assessment and intervention represents a promising direction in the comprehensive management of this condition.

Further research is needed to elucidate the mechanisms by which psychogenic factors contribute to the development of alopecia. An increasing body of experimental data highlights the role of neurogenic inflammation in modulating immune responses in alopecia areata (AA), particularly through the release of neurotransmitters.

Among the key mediators involved in stress-induced disruption of hair growth is the neurotrophin nerve growth factor (NGF), which plays a significant role in stress response, psychological processes, immune regulation, and hair follicle biology [10,11,23].

In this context, further investigation into the role of psychosomatic disturbances and clinical characteristics of alopecia in modulating NGF levels is warranted, particularly in AA, an autoimmune condition traditionally classified among classical psychosomatic diseases, in which stress plays a critical role in disease initiation and progression [12,27].

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