

# PSYCHONEUROIMMUNOLOGY AND IMPACT OF STRESS IN CHRONIC SKIN CONDITIONS

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## ABSTRACT

Psychodermatology studies the relationship between skin and mind. The important starting point in most of the chronic skin conditions is the psychological factor. Acute adverse events are classic triggers for these diseases. Chronic distress plays an important role, especially in time of public professional and financial instability, combined with the characteristics of the personal profile of the individual. Patients suffering from chronic skin dermatoses are tense, anxious, and unable to relax. This article reviews the neuro-endocrine pathways in the genesis of psychodermatological conditions. The paradigm: chronic skin conditions, stress and psyche is discussed. The review is based on the data from English language literature using MEDLINE and PubMed.

**Keywords:** *psychodermatology, stress, psychoneuroimmunology*

## INTRODUCTION

The first who coined the term “stress” was the Austrian-Canadian endocrinologist Hans Selye. He discovered and documented that stress differs from other physical responses in that whether one receives good or bad news, whether the impulse is positive or negative it’s still stress. He called negative stress “distress” and positive stress “eustress”(1). In 1977, Selye emphasized that the body is in a state of readiness to respond to external influences.

Psychosomatic dermatoses are those skin conditions in which an important role is played by the

psyche. It should be noted that in most of the cases it is not clear what the sequence of their occurrence is. Undoubtedly these diseases impair most severely the quality of life and are difficult to treat. Understanding the physiological and immunological basis of psychosomatic paradigms, such as skin, stress, brain is essential for the study of these diseases.

### *Chronic Skin Conditions, Stress and the Psyche*

The connection between skin disease and neurotic or psychological influences has been known for more than a century (2). The imaginary relationship between the skin and the psyche from earlier scientific papers (3) later turned into a theory that a psychological component plays an important role in the pathogenesis of many skin conditions (4). For a long period of time the term neurosis has been attributed to conditions with impaired nerve function without a structural pathology. Later the prefix “psycho-” was added for a functional disorder in which feelings of anxiety, obsessional thoughts, compulsive acts, and physical complaints without objective evidence of disease, in various degrees and patterns, dominate the personality (5).

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It is an indisputable fact that many of the chronic skin conditions have a primarily psycho-neurogenic origin (6). These dermatoses occur and flare from various stressful situations - during or after strong or mild but prolonged periods of mostly negative emotions.

Classic examples of psychosomatic diseases are chronic pruritic dermatoses such as prurigo nodularis, pruritus sine materia and neurodermatitis. The constant itching that accompanies the clinical picture has not only physical but also psycho-emotional effect on the patients, implicating them in the principle of feedback, which exacerbates the skin condition (7). Another typical representative of psychosomatic diseases is atopic dermatitis (AD). The connection between AD and the emotional state is not new. Brunsting (1936) (8), Alexander (1950) (9), and Graham (1952) (10) are among the first authors who pointed out the psycho-neurogenic origin of AD. Dave et al. (2012) discussed the relation between psychological stress and allergic diseases. They underlined that the course of the disease is more severe in patients exposed to stress (11). Stress is pointed out as a major trigger of other wide spread dermatoses, such as psoriasis vulgaris. In their article Kalman et al. (2014), with regard to the stress as a causative agent for the developing and exacerbation of psoriasis, insisted that this correlation is closely linked to the individual characteristics of patients (12).

In a large group of dermatoses itch as a leading symptom is an additional source of stress, but the other large group of skin conditions in which stress is equally the output and consequence of the disease should also be mentioned. That is the group of disfiguring skin conditions and facial dermatoses. Manolache and Benea (2007) study the role of stress before and during alopecia areata and vitiligo (13). They point out that stress has a significant influence on the onset and deterioration of both skin conditions. These data are also confirmed in other studies (14,15).

### **Classification of Psychodermatological Conditions**

The relationship between the dermatological conditions and psychological factors has been studied for a long time. Recently the interest in this area has been greatly increased (16). In the past, psycho-

dermatological phenomena were classified on the basis of individual specific links between the skin symptoms and the personality characteristics of the patient (17). Later, a generalized classification was offered. According to this classification, three categories of psychodermatological diseases have been differentiated (18). Psychophysiological (psychosomatic) disorders is a group of diseases and conditions that depend on the genetic and/or environmental factors, but where the course of the disease is greatly affected by stress. The second group consists primary of psychiatric disorders, which lead to self-induced skin diseases. The third group includes secondary psychiatric disorders caused by disfigured skin, which can lead to states of fear, depression or suicidal thoughts (19). The division of chronic skin conditions related to stress is illustrated in Table 1.

*Table 1. The division of some of the chronic skin conditions according to their relation to stress (18).*

Psychophysiological (psychosomatic) disorders	Psoriasis vulgaris Eczema Lichen simplex chronicus Atopic dermatitis Acne
Primary psychiatric disorders leading to self-induced skin disease	Trichotillomania Acne excoriata Delusions of parasitosis Venerophobia
Psychiatric disorders caused by disfiguring skin	Acne conglobata Alopecia areata Icthiosis Vitiligo Rosacea

As shown in Table 1, some of dermatoses could be attributed to more than one of the groups. This confirms that psychogenic factors and stress are both the potential cause and consequence in the course of skin conditions.

### **The Psychological Impact of Stress-Related Skin Conditions**

Hiller (1865) emphasizes the influence of mental excitement, nervous instability and anxiety on the development of various dermatoses (20). He is the first who pointed out the relationship between stress and the skin. In 1982 Teshima et al. found that

emotional stress can greatly affect the immune system and this is manifested in the development of various dermatoses (21). It was underlined that the emotional pressure in the patient leads to enhancement of the skin reaction and these patients showed improvement after relaxation (17).

The studies on the psychological impact of skin diseases are not new (17-19). Extensive researches in this area reveal a wide range of psychological effects associated with numerous dermatoses and skin conditions (21). These include depression, sexual problems and problems with communication. There are also reports that these patients are subjected to greater psychological and social stress (7,16). Thus, patients with neurodermatitis report that their disease has various adverse effects on their daily rhythms of life (22). Many patients indicate that the disease interferes with their sexual relationship and communication with partners (23). Chodkiewicz et al. (2007) report that patients with rosacea are less satisfied and have a higher level of anxiety and depression in comparison to healthy subjects (24). In another large study conducted among 807 patients from four countries, high rate of depression and fear from social contacts in patients with facial dermatosis was established (25).

There is no doubt that emotional stress affects a wide range of medical conditions. But the question of why under the influence of stress different diseases develop is still under discussion. According to different studies the prevalence of psychological factors with an impact on skin diseases varies from 25% to 33% (26). Furthermore, there is no irrefutable evidence that stress affects the normal functions of the body. The diathesis-stress model is the basis of the biopsychological model and focuses on the relationship between the predisposition to disease, the diathesis, and the environment and the stress (27).

#### ***Psychoneuroimmunology. Responses to Stress***

It is known that the skin and nerves have the same embryonic origin (28). The central nervous system, the peripheral nervous system, the peripheral nerves and the skin structures, melanocytes and Merkel cells originate from the common neural crest. The functional relationship between the brain and the immune system is established through the connection between the autonomic nervous sys-

tem and the neuroendocrine one in the hypothalamus and the pituitary gland. The communication between the brain and the immune system is bilateral and widely mediated by neuropeptides (29). The neuro-endocrine-cutaneous immune system is considered to be a part of an integrated system, determining the behavior of the organism against neuroendocrine and immune function (30).

The skin plays an important immunological function, involving a large amount of cells in coordinating the body's response to external and internal disturbances (31). Glycoproteins termed cytokines play a major role in mediating this process. They are produced by various cells in all organs and systems. In general, they are divided into interleukins (IL), colony-stimulating factor (CSF), interferon (INF) and tumor necrosis factor (TNF) (32). After the connection with specific receptors cytokines modify the processes of inflammation, proliferation, and immune responsiveness in target cells. The cytokines can inhibit or stimulate the production of other classes of cytokines. They also have a huge impact on Th lymphocytes in the process of differentiating and participating in cell-mediated (Th1) or humoral immune response (Th 2) of the body (33).

The skin is a huge exteroceptor. The skin sensitivity involves the perception of sensations of touch, temperature fluctuations and pain. This physiological process includes acceptance of the irritation, which means that the external triggers have been transformed into nerve impulses followed by the conduction to various departments of the central nervous system through afferent nerves and finalized by analysis in the cerebral cortex. The perception of sensations is performed by structures which could be found in the skin: the lamellar corpuscles of Vater-Pacini, the inclusion bodies of Wagner-Meissner and free nerve endings (34). The sensations are transmitted through the ascending spinal nerves by myelinated A $\beta$  fibers, A $\delta$  fibers and unmyelinated C-fibers or through the cranial nerves to the thalamus and the cortex. Some of these unmyelinated C-fibers also secrete neuropeptides and thus participate in the efferent response of the body (35). These substances are a heterogeneous group of peptides and amino acids. They play the role of messengers between the cells, which, alone or in groups, impact the neuroendocrine and immune elements of the body's response

to the acute or chronic stress (36). The level of functional response of the irritant perceived as stress depends on the individual perception of the magnitude and the importance of the irritation. The level of efferent response is defined by factors, which may inhibit or aggravate the reaction (37).

The body has the ability to adapt to the sudden changes in the status (38). At the same time chronic stress can lead to a state of helplessness and chronic irritability (39). The response to the stress depends not only on the type of irritation, but also to the subjective attitude of the patient. Jacobs et al. (1966) underlined that individual characteristics and mode of dealing with irritants modify the body's immune response to stress. The authors pointed out that persons classified as passive, negative, easily excitable and impulsive have a weaker adaptive abilities and weaker skin reactivity (40). In a comparative study Janner et al. (1988) found lower levels of monocytes and higher levels of eosinophils in the patients with anxiety compared to those with stable psyche when exposed to stress (41). Millard (2005) underlined that stressful events stimulate the autonomic, neuroendocrine and immune answer of the body (42). He suggested a classification of the most common stress-producing events (Table 2) (42).

Table 2. Events producing stress (52)

Emotional	Fear, rage, anger, helplessness, frustration
Environmental	Changes in temperature, noise, daily rhythms
Personal	Insulation, dietary changes, withdrawal, extreme starvation, hierarchical challenges

Regardless of the type of stressful event the response is a start of the neuroendocrine pathway through the hypothalamic-pituitary-adrenal axis (43). As a result to stressors the endocrine system increases secretion of corticotropin-releasing hormone (CRH) from the hypothalamus and sympathetic stimulation of the adrenal medulla. CRH activates ACTH secretion from the anterior pituitary, resulting in stimulating cortisol from the adrenal medulla. The next step is the increase of epinephrine and norepinephrine secretion (44). Both epinephrine and cortisol increase the blood glucose levels and the release of fatty acids from adipose tissue and the liver. At the same time, sympathetic innervation of the pancreas decreases insulin secretion. Consequently,

most tissues do not readily take up and use glucose. In this way the nervous system is available primarily to use glucose. The fatty acids are used by skeletal and cardiac muscle, and other tissues. Cardiac output and blood pressure are increased by epinephrine and sympathetic stimulation (45). Finally they act on the central nervous system and increase alertness and aggressiveness. The initial inflammatory response is decreased by cortisol. The close connection between the nervous and endocrine systems is proved by the response of the body to stress (37).

### *Neuro-Endocrine Pathway in the Genesis of the Disease*

During the neuroendocrine response, ANS is activated by the parts of the brain stem, mostly of the cerebellum, which provokes the production of norepinephrine and neuropeptide from spinal ganglia and adrenal medulla. These neuropeptides released from ANS, have a control over neurons secreting corticotropin-releasing factor (CRF) and brain centers for pain sensation. The CRF1 receptor in the brain is closely connected with stress-related changes in behavior including anxiety and depression (46).

Neurohormones are hormones produced by neurosecretory cells and released by nerve impulses (e.g., norepinephrine, oxytocin, and vasopressin)

(47). The neurotransmitters and neurohormones which take part in the neuroendocrine pathway of the disease are mainly neuropeptides with short chains containing up to 40 or less amino acids. These include substance P (SR), calcitonin gene related peptide (CGRP), and vasoactive intestinal peptide (VIP) (48). Other important neuropeptides are neurokinins A and B, neuropeptide Y, somatostatin, and opiomelanocortins, including endorphin (47).

The chronic immune response to the stress is the immunosuppressive reaction (49). It is mediated by triggering a change in the response of T-helper cells. It is known that the main function of Th1 cell is to promote cell-mediated immunity in Th2.

These cells are mainly connected with the humoral immune response of the body (49).

In the condition of chronic stress catecholamines are released. They influence the process further by inhibiting IL12 and increasing the levels of IL10 (50). Furthermore, it has been assumed that the response to the acute stress situation that occurs in chronic dermatoses is induced by catecholamines and corticosteroids (49). These stress hormones act by increasing the cell-mediated immunity through INF gamma and the cytokine IL2.

Edna Reiche et al. (2004) pointed out that there is plenty of evidence for both stressors and depression, which may induce a disorder of the immune status by decreasing the activity of cytotoxic T-cell and natural killer cells and producing proinflammatory cytokines including IL6 (51). In a report that analyzed more than 300 empirical articles, Segerstrom et al. (2004) show that chronic stressors were associated with suppression of both cellular and humoral immunity (52). Constant increase in the levels of proinflammatory cytokines can lead to numerous chronic dermatoses. It is clear that the negative emotions directly attack the immune system through stimulation or suppression of the immune response by inflammatory cytokines.

The major stressors related to chronic skin conditions are: itching, sleep disturbance, withdrawal of touching, fear of allergies, changes in diet, psychosexual problems and others (53). The influence of these factors depends on individual and generic characteristics.

Increased levels of Th2 compared to those of Th1 have been observed. This results in increased humoral immunity through the action of cytokine IL4. This leads to activation of B cells and increases the activity of eosinophils through cytokine IL5 (53). The induction and maintenance of eosinophils is performed by Th2 cytokines. Thus the additional chemokines, which participate in attracting immunocompetent cells to the skin, are produced. These include eotaxin, thymus and activation related chemokine (TARC) and regulated on activation, normal T-cell expressed and secreted (RANTES). Other cells, which are involved in this process, are mast cells. Their degranulation leads to release of histamine, which has local vasoactive and inflammato-

ry effect on the skin. Lonne-Rahm et al. (2008) investigated eleven patients with atopic dermatitis with history of stress. The authors found an increase in mast cells, serotonin receptor subtypes 5-HT1A and 5-HT2A, and serotonin transporter protein (SERT) in the involved skin (54). Furthermore, the direct impact of neuro immunocutaneous system through C fibers activates the release of neuropeptides SP, CGRP, VIP and neurogenic factor (NGF) (55). In 2003 Järvikallio et al. studied the association between mast cells and sensory nerves and the distribution of the neuropeptides substance P (SP), vasoactive intestinal polypeptide (VIP) and calcitonin gene-related peptide (CGRP) in lesional and non-lesional skin of 26 atopic dermatitis and 23 nonatopic nummular eczema (NE) patients. They found out an increased SP-positive and CGRP-positive fibers associated with increased mast cell-nerve fiber contacts in atopic dermatitis lesions (56). Stressors induce a proliferative response in leukocytes, monocytes, keratinocytes, dermal dendritic cells, eosinophils and mast cells (57). Cytokines promote Th2 responses, especially IL10, which is a strong immunosuppressant of the Th1 helper cells (16). The catecholamines secreted after stress also participate in the pathogenesis of neurodermatitis, psoriasis and eczema. This process is mediated by beta adrenoceptors on the cells. The intracellular phosphodiesterases are enhanced to degrade cAMP and produce cytokines IL4 and IL13 (58).

## CONCLUSION

The paradigm of chronic dermatoses, stress and mentality underlies the understanding and management of psychosomatic skin diseases. The psychological factor is an important starting point in both disfiguring skin conditions and pruritic chronic dermatoses. Chronic distress plays an important role in the whole course of the disease. It starts a complicated psychoneuroimmunological cascade. The interruption of this pathway is a difficult process and should be the main goal of treatment.

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