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Psychological Stress in Patients with Atopic Dermatitis

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ABSTRACT Atopic dermatitis (AD) is a frequent dermatosis with a growing incidence and multifactorial and complex pathogenic mechanisms that are still being investigated. Although the connection between AD and psychological stress has been known for a long time, there is a lack of reliable and objective indicators for the characterization of this association. Psychological stress triggers complex immune pathways. Therefore, acute stress quickly triggers a high release of cortisol and adrenalin or noradrenalin which then stimulates the immune system, primarily T-helper type 1 (Th1 cells) to produce pro-inflammatory cytokines, resulting in a cellular immune response and inflammation. On the other hand, chronic stress increases basal cortisol levels and decreases the capacity to mount an acute stress response, with the immune system shifting from a cellular response (which is active in acute stress) to a humoral response. Furthermore, skin keratinocytes contain receptors for neurotransmitters and hormones (muscarinic, adrenergic, glucocorticosteroid, androgenic, estrogenic), thus actively participating in psychoneuroimmunological pathways. The measurement of plasmatic cortisol has been used routinely, but in recent years, particularly in research, preference has been given to measurement of salivary cortisol. Reliable psychological tests are an important additional parameter for assessment of a patient's psychological state. We hope that future studies will supplement our current knowledge on the influence of psychological stress in AD.

KEY WORDS: atopic dermatitis, psychological stress, cortisol, immune factors, psychoneuroimmunology

INTRODUCTION

Atopic dermatitis (AD) is a chronic dermatosis with very diverse clinical manifestations. It is characterized by dryness, recurring skin changes with erythema, and eczema followed by intense skin itching; it is associated with immediate allergic hypersensitivity (atopy) and delayed hypersensitivity (1-4). Our present knowledge suggests that AD can be caused by multiple factors, such as genetic predisposition, various allergens, disorders of the humoral and cellular immune responses, disorders of the epidermal skin barrier, neurovegetative factors, climate conditions, stress, etc. (2,3). Due to the increasing prevalence of AD and the growing expenses required for its treatment, extensive research efforts have been made in order to obtain a deeper insight into this disease its pathogenesis in particularly, since this could be important in the treatment of patients with AD. Although the connection between stress and AD has been studied over the years, there is currently great interest in the analysis of the influence of stress on AD

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manifestations, especially when considering recent psychoneuroimmunology research. Of the various etiological factors which may affect AD, there is still a high interest in analysis of the influence of stress, especially when considering recent psychoneuroimmunology research.

Stress and atopic dermatitis – historical data

When the impact of stress on the manifestations of AD was monitored in patients with AD, deterioration of the clinical picture was observed and the impact of emotional factors on the severity of the disease was demonstrated (5). However, as no general consensus on the influence of stress on AD has been reached, the need has arisen for achieving deeper insight into the fundamental psychobiological mechanisms and the ways in which stress can influence AD (6).

The connection between the AD manifestations on the one hand and emotional factors and stress on the other was noticed and described at the very beginning of the research and monitoring of patients with AD. Early in the last century, AD and asthma were primarily considered to be psychosomatic diseases: as late as 1950, Alexander (Psychosomatic Medicine) describes them as typical representatives of such diseases. Gradually (in the 1930s and 1940s), the viewpoint that the AD etiology was of a multifactorial nature started to spread, the argument being that emotional factors were only one of the triggers contributing to the manifestation and aggravation of the disease (7). Later, in the 1970s and 1980s – even in the 1990s – studies on the connection between AD and emotional stress focused on the personality traits, or "psychological profiles", of atopic patients (8-14).

Thus, in the 1970s and 1980s, numerous studies of patients with AD reported increased anxiety, depression, anger, and hostility, particularly in correlation with the severity of their clinical AD manifestations. However, these studies were of questionable quality because they included small groups of patients, and controls were rare. So the question remains whether the psychopathological results of the research were elucidating of the pathogenesis or whether they were an epiphenomenon of a chronic inflammatory disease (15). In the late 1990s and in the 2000s, the research – primarily in immunology (psychoneuroimmunology and psychoneuroendocrinology) – led to important new discoveries, renewing discussions of the influence of stress on the manifestations and severity of AD (6,16-26).

The mechanism of stress impact on atopic dermatitis

The research results and insight into psychoneuroimmunology obtained thus far strongly confirm that stressful life events have a substantial impact on the functioning of the immune system (27-29). In this context, the hypothalamic-pituitary-adrenal axis (HPA) has an important role in the complex response to stress. It is well known that stress stimulates the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus. By means of circulation, CRH reaches the pituitary gland and stimulates the secretion of adrenocorticotropic hormone (ACTH), which, in turn, affects the adrenal cortex and stimulates the secretion of cortisol (28). Cortisol is the main glucocorticoid produced in the fasciculate zone of the adrenal cortex, where it is synthesized from cholesterol, and which has an effect on the inflammatory reaction. It strongly suppresses overall inflammation and, consequently, its values increase during stress – not just acute, but also chronic stress (30-32). Acute stress may induce an individual's adaptive response to environmental demands, while chronic, excessive stress causes cumulative negative impacts on health outcomes through "allostatic load" (32). Therefore, the measurement of chronic stress mediators provides a timely opportunity for prevention or earlier intervention of stress-related AD.

Acute and chronic stress have different impacts on the immune system (15). Acute stress triggers, within only a minute, a high release of cortisol and adrenalin or noradrenalin which then stimulates the immune system, primarily T-helper type 1 (Th1) to produce pro-inflammatory cytokines, including IFN-γ, resulting in cellular immune response and tissue damage (15,33,34). This cortisol secretion in acute stress also serves as protection and as an anti-inflammatory mechanism for maintaining homeostasis (35).

On the other hand, chronic stress exposure increases basal cortisol levels along with decreasing the capacity to mount an acute stress response. In this state the immune system shifts from a cellular response (which is active in acute stress) to a humoral response with a prominent role of cytokines (15). The pathogenesis of AD, as a chronic allergic disease, includes this switch to a humoral immune response which is one of its crucial pathogenic mechanisms (6,33-35). This enables the immune system to facilitate development of autoimmune and atopic diseases. Studies show that epigenetic modification of the HPA stress axis makes the individual even more susceptible to manifest imbalanced chronic stress

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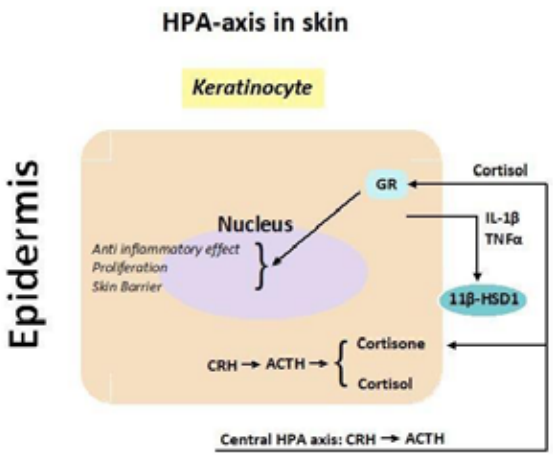

Figure 1. Skin hypothalamic-pituitary-adrenal (HPA) axis – the mechanism of stress influence on the HPA axis and the immune system (according to Lin TK, et al., 2017) (35).

response (15). Patients with chronic AD have HPA dysfunction, presenting with an attenuated cortisol responsiveness after stress exposure which may be a reason for the imbalance between humoral and cellular immune response (6). Chronic stress exposure leads to a slower rise of morning cortisol and a baseline secretion of cortisol.

Another important fact for understanding the connection between the skin and psychoneuroimmunological pathways is the fact that skin keratinocytes contain receptors for neurotransmitters and hormones (muscarinic, adrenergic, glucocorticosteroid (GC), androgenic, estrogenic) (36,37). During stress, ACTH secretion-stimulated CRH production promotes the generation of pro-inflammatory cytokines in skin keratinocytes, resulting in T-cell activity stimulation (38-41). This supports active roles of skin cells and other skin structures in inflammation.

In addition to the above-mentioned central HPA axis, there is a peripheral (skin) autonomous HPA axis stress regulation (as important as the central HPA axis) which exists to regulate its homeostasis in response to its ongoing exposure to environmental stressors (Figure 1) (35). According to the latest knowledge, the skin (peripheral) HPA axis plays an important role (35). Under stress, skin keratinocytes produce CRH, ACTH, and cortisol. It has been confirmed that keratinocytes synthesize cortisol with the help of the 11 beta-hydroxysteroid dehydrogenase (11beta-HSD) enzyme which activates cortisol from cortisone. Furthermore, cortisol impacts the immune system by increasing Th2 cell activity in chronic stress exposure and by regulating skin keratinocyte activity, inducing anti-inflammatory effects and disrupting skin barrier homeostasis (6,35,41).

However, the components of this neuroendocrine system have been described for many structural cells of the skin (e.g. melanocytes, sebocytes, fibroblasts, etc.), although they have been particularly well characterized for keratinocytes. It has been reported that all regulatory elements of the central HPA axis are also expressed in mammalian skin, including CRH, pro-opiomelanocortin (POMC) derived peptides, *GCs,* and related peptides, as well as their appropriate functional receptors, CRH receptors, melanocortin receptor type 2 (MCR2, the classical adrenocortical ACTH receptor), and GC receptor NR3C1 (35). This skin axis shows a similar hierarchical structure to the central axis.

Along with HPA central and peripheral axis, there is another important effector pathway of stress regulation that involves the sympathetic nervous system (SNS). Stimulation of the SNS results in the release of catecholamines (adrenalin and noradrenalin) from the adrenal cortex and sensory nerve endings (28). It is also important that skin cells have receptors and react to neurotrophic factors, predominantly keratinocytes but also lymphocytes, macrophages, eosinophils, and mastocytes (20).

Substance P and NGF, as a part of another skin stress response pathway, are detectable in increased levels in animals affected by systemic and local stress (38). This pathway is called the neutrophine neuropeptide axis (NNA) (15). Substance P is released in the skin from peripheral nerve endings and induces infiltration of inflammatory cells and TNF, IL-1, IL-6, and IL-12 cytokine production (38). It is also responsible for triggering an immune system shift to a chronic stress response in which the HPA axis is dysfunctional (35). Another part of this pathway is neutrophine NGF which directly affects keratinocyte proliferation and immune cell reactions in inflamed skin (38). Activation of this pathway in response to exposure to environmental stress showed worsening of the skin pictures as observed in animal studies of AD (23). Together, these pathways of stress regulation alter the neuroendocrine and inflammatory stress responses (15).

The results of the psychoneuroimmunological research carried out so far can be viewed as a strong confirmation that stressful events in life are substantially associated with the functioning of the immune system (20,23,25-30,35). Some clinical studies examining the effects of stress on AD manifestations supported a strong bond between them. The studies discussed below provide strong evidence supporting these connections. The study carried out by Kodama *et al.* (on 1,457 respondents) established a connection

between natural disaster (earthquake) and AD; aggravations in three groups were established, depending on the level of exposure (in a severely damaged area – 38.4%; in a lightly damaged area – 29.1%; in an undamaged area – 7.0% of patients) (39). Mizawa *et al.* also studied the connection between stress and the seriousness of clinical AD manifestations (40). Their measurements of salivary cortisol as a stress parameter and life quality test (Skindex 16) demonstrated the impact of stress on AD manifestations.

Laboratory methods of stress determination

However, the real impact of stress on AD manifestations is still relatively unknown, primarily due to a lack of methods that would objectify and measure stress and the lack of reliable parameters that would help assess true levels of stress in these patients. There are several possible diagnostic methods, predominantly serum cortisol and, as of late, saliva.

Stress level determination by serum cortisol

Although both acute and chronic stress can be quantified through measurement of changes in physiological indicators (e.g. heart rate, blood pressure, levels of metabolic hormones), it is unclear whether we can interpret the changes in serum cortisol as reflecting acute, chronic, or daily stress variations (32). In general, acute cortisol levels fluctuate markedly depending on many physiological factors (e.g. circadian rhythm) and may provide a rather poor reflection of normal, chronic cortisol secretion.

Cortisol secretion in response to stress contributes to the suppression of the HPA axis which generally affects health and cognition (32). Since many cortisol actions rely on binding to cytosolic receptors, only a small fraction of unbound, free cortisol is biologically active. In general, serum cortisol levels increase during the early morning (highest at about 8 AM) and decrease slightly in the evening and during the early phase of sleep, so the timing of blood sampling is very important (32).

Serum cortisol remains high during the circadian cycle and under different dynamic tests such as ACTH stimulation. A high correlation between salivary cortisol levels and unbound cortisol in plasma and serum has been confirmed.

Stress level determination by salivary cortisol

Since free cortisol represents only a fraction of the biologically active hormone, salivary cortisol measures have been considered a better method for the evaluation of adrenocortical function (32). Thus, saliva is an appropriate material for an assessment of stress levels in patients. Salivary cortisol values are used for the assessment of acute and chronic stress and have been in use for some 30 years now (40-46). It is known that cortisol levels in saliva serve as an index of acute psychological stress, while being a useful index for the assessment of chronic stress (43,44). Furthermore, taking saliva samples is a non-invasive method that enables gathering of a large number of samples in a simple way with no discomfort for the patient. The research so far has shown a very good correlation between the salivary and plasmatic cortisol. In adults, the correlation is approximately 0.75 (46).

However, numerous factors can affect measurement results of salivary cortisol values (45-47). The sex of a patient can impact readings through monthly sex hormone cycles, menstrual cycles, hormonal contraception usage, pregnancy, breastfeeding, puberty, menopause, and possible variabilities in the salivary cortisol results. However, they cannot be excluded from the sample because it would result in the loss of generalizability. Furthermore, the time of sampling is important: the smallest number of fluctuations is expected late in the afternoon and the maximum concentration in the morning (7-10 AM). The time a person wakes up, on the other hand, has no relevant effect on the morning response of cortisol (47). Other factors that can affect the result include intensive physical training, high-energy foods, smoking, coffee, alcohol, certain medicines (CSs, psychoactive medicines, antidepressants), and psychological factors (the ability to deal with stressful situations, social support, etc.). These are all the potential sources of the variance. However, ruling out the potential variances would lead to model overlapping and, consequently, to false results. This is why as many samples as possible should be taken (27).

Factors important for stress measurement in patients

Both serum and salivary cortisol levels reveal acute changes at a single point in time, but the overall chronic systemic cortisol exposure is difficult to evaluate due to circadian variations and its protein-binding capacity (32). A newer and highly promising technique is the analysis of cortisol in hair, which assesses chronic stress retrospectively. However, salivary cortisol may have some advantages over the assessment of serum cortisol, while cortisol assessment in sweat or tears is only of theoretical importance and urinary cortisol is of decreasing interest in diagnostics (32).

According to recent research, a weak response of the salivary cortisol was recorded in patients with AD (children and adults) under strong psychosocial stress (in other words, lower values of the salivary cortisol were recorded), indicating hypofunction of HPA axis (48). At the same time, a weak reaction of the HPA axis was observed during intense stress, which is a possible explanation for the deterioration of AD symptoms as a result of stress.

The fact is, the response of the HPA axis is rather complex; it is modulated by numerous factors, which can affect diagnostics and diagnostic results. Therefore, a patient's subjective stress experience and their reaction to stress are very important for the stress evaluation and its effect on the disease. Psychological tests are helpful as they constitute an additional, very valuable evaluation parameter, particularly compared with objective lab indicators such as cortisol. The importance that a patient attributes to their disease has a stronger influence on their perception of the disease than the (real) severity of the disease as such (49). It is also important to keep in mind that stress is a provocative factor, but is also a consequence of AD.

In addition to visible changes on the skin and the impact of psychological effects, patients with AD face another problem – itching. The patients primarily identify its intensity with the severity of their disease (instead of the intensity of the skin changes). Itching disturbs the sleeping cycle, thus completing the circle of stress as both a cause and a consequence of AD. Psychological tests are an instrument we can use to distinguish acute stress from chronic stress and causal stress from resultant stress.

In addition to the influence of stress on AD, an adverse effect of AD on the psychological functioning and quality of life of the patients has also been observed and described thoroughly in the literature (49). It is also important to emphasize that a patient's perception of their disease is strongly influenced by their own experience, which the patient attributes to their condition more than to the severity of the disease as such. The obtained psychoneuroimmune data strongly confirm a striking connection between life under stress (e.g. due to bereavement, excessive workload, or a strong concern about others) and the functioning of the immune system. This complex process may have an influence on AD manifestations and the clinical picture.

CONCLUSION

There are many valuable arguments that show a strong connection between psychological stress exposure and occurrence of skin lesions in patients with AD. Many pathways that are active when the body is under psychological stress may contribute to changes in the patients' clinical pictures, including HPA axis stimulation and dysfunction, along with the neuroendocrine system pathways and neurotransmitters released in the skin. In diagnostics, aside from measuring serum cortisol, the measurement of salivary cortisol has been increasingly used as a non-invasive technique that ensures very good correlation to plasmatic cortisol.

Taking the above into consideration, there is still a lack of clinical studies with precise multiple diagnostic procedures that prove a reliable stress influence. As precise pathogenic factors and lab indicators during psychological stress need to be elucidated, we hope that future studies will supplement current knowledge of the influence of psychological stress in AD**.**

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