

Anxiety in allergy and atopic dermatitis

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Purpose of review

Individuals suffering from allergies often exhibit a specific psychological profile characterized by anxiety, depression and emotional excitability. Emotional stress precipitates allergic symptoms not only by heightening anxiety levels but also by dysregulating immune-cell functions. The primary objective of this report is to review recent findings of the relationship between anxiety and hypersensitivity responses in the context of psychoneuroimmunology in allergic individuals, notably patients with atopic dermatitis.

Recent findings

Atopic subjects with emotional problems develop a vicious cycle between anxiety and clinical symptoms. Acute stresses, which repeatedly and chronically affect patients with atopic dermatitis, raise anxiety in general more preferentially than anxiety at present. This psychological failure enhances Th2-type responses due to dysregulation of the neuroimmune system, leading to worsening of allergic symptoms. Tansospirone, a 5-hydroxytryptamine 1A receptor agonist with anxiolytic and antidepressant effects, attenuates itching through successful control of emotional difficulties. These data suggest the efficacy of administering drugs with anxiolytic effects as part of the management strategy of stress-associated itching in patients with atopic dermatitis.

Summary

Psychological interventions such as periodic monitoring of anxiety levels in the context of immune functions and skin conditions are fundamental in therapy of allergic patients with emotional problems.

Keywords

allergy, anxiety, atopic dermatitis, psychoneuroimmunology, stress

Introduction

The endocrine, nervous and immune systems continually communicate with each other through interaction of critical cells able to receive information from each system [1,2^{*}]. Homeostasis, and thus overall health, is maintained under optimal conditions in which these systems work in harmony. Individuals feel stressed when there is disruption of the psychological equilibrium between the demands of life and coping skills. At the same time, quick mobilization of the endoneuroimmunological network allows us to cope with stress. A well known characteristic of stress-axis functioning is the marked individual differences in susceptibility to challenge [3,4^{**}]. In most individuals, acute stress is adaptive and protects the body; however, others respond in such a way that homeostasis is perturbed and health is negatively affected by distress, depression and anxiety. Furthermore, the day-to-day load of acute stressors can generate chronic stress, resulting in long-term damage due to dysregulation of homeostatic neural, endocrine, and immunologic mechanisms.

The fundamental features of atopy are biological and psychological hypersensitivity [5,6]. In biological hypersensitivity, immune responses occur as a result of otherwise harmless external and internal stimuli. In individuals with atopic diathesis large amounts of IgE are produced in response to tiny quantities of allergen, and, as a consequence, IgE-related allergic responses are triggered systemically and locally through activation of Th2-type immune cells. Psychological hypersensitivity refers to a reaction to nonallergic sensory stimuli rather than biological triggers. One such response is elaboration and reinforcement of anxiety by stress. Since exacerbations of allergic symptoms are often preceded by emotional reactions, the relationship between psychological factors and allergy has long been investigated in the context of psychoneuroimmunology. This brief paper reviews the interaction between psychological stress and anxiety and the immune system in the context of modification of allergic symptoms in atopic dermatitis patients.

Stress and allergy

Neuroendocrine and autonomic nervous systems are the representative pathways through which the central nervous system exerts control over the immune system. Neuropeptides released by the brain act directly on immune cells or indirectly by releasing hormones such as glucocorticoids through the hypothalamus–pituitary–adrenal (HPA) axis [1,2^{*},3,4^{**}]. The central nervous system can also regulate immunity via efferent

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Abbreviation

HPA hypothalamus–pituitary–adrenal

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autonomic nervous connections by releasing norepinephrine and epinephrine. Functional balance of these systems is critical for maintaining homeostasis, and loss of balance due to psychological stress results in release of excess amounts of adrenal glucocorticosteroids and catecholamines into the circulation and tissues. Since the effect of these stress hormones on immunity seems to be selective, more preferentially affecting the function of Th1 cells than Th2 cells, immune responses are skewed toward the Th2 phenotype [7,8]. Thus, in allergic individuals, worsening of clinical symptoms might ensue due to enhancement of Th2-related immunity.

Stress also influences the development of immune function in childhood [9^{••}], with persistent parental and caregiver stress having been shown to be critical. Chronic stress in children results in progressive downregulation of the reactivity of the HPA axis in later life, and children predisposed to atopy can ultimately become ill because of intense Th2 polarization. Demonstration of neuroendocrinological control over immunity in neonates from an atopic family [10] also confirmed that later development of atopic symptoms can occur due to debilitating effects of chronic stress on the HPA axis.

Psychological profiles of atopic dermatitis patients

The effect of allergic disorders is multidimensional, affecting physical, social, and psychological health. Atopic dermatitis understandably leads to psychological disturbances such as stigmatization, social isolation, and discrimination because of the instinctive aversion to skin disease [11]. Furthermore, many patients become frustrated by the perceived ineffectiveness of their therapies. As a result, they tend to have a lower health-related quality of life and greater psychological distress than individuals with other medical conditions.

Both children and adults suffering from atopic dermatitis often exhibit a specific psychological profile characterized by anxiety, depression, emotional excitability, and inactivity [12,13]. In addition, children with atopic dermatitis often have behavioral problems such as increased dependency, fearfulness, and sleep difficulties. Whereas psychological activation levels are high regardless of disease activity, mental responses to stress are no stronger in atopic dermatitis sufferers than in normal individuals [14[•]]. It remains unclear whether such psychological profiles are premorbid with etiological significance, or whether a reactive personality arises as a consequence of the experience of illness. A semiometric study of allergic patients revealed psychological divergence, whereby atopic dermatitis sufferers have a unique persona profile that differs from those of asthmatics and rhinitis patients [15]. Furthermore, it has been shown that anxiety in

atopic dermatitis is not a result of the burden of having a chronic skin disease [16]. These findings suggest that these psychological characteristics are stable in atopic dermatitis, and cannot be attributed solely to increased disease activity.

Stress and atopic dermatitis symptoms

Both acute and chronic stresses associated with major life events as well as minor everyday difficulties contribute to the likelihood of an atopic dermatitis episode. In female patients, premenstrual syndrome, which manifests as irritability, anger and depression, is also closely associated with symptomatic deterioration in atopic dermatitis [17]. The relationship between psychological stress and atopic dermatitis symptoms seems to be bi-directional, since on one hand stressors often exacerbate skin conditions while on the other worsening of cutaneous signs lowers the stress threshold. It is likely that the sympathetic nervous system plays a pivotal role in this setting, preventing many patients from resting due to sympathetic overactivation. Subsequently, this generates further stress, increasing activation of the nervous system. As a result, a vicious circle of emotional stress and skin conditions can be initiated, leading to chronicity of atopic dermatitis symptoms. Another example is the anxiety felt by mothers as a result of atopic dermatitis in children, and vice versa, which creates a vicious psychological cycle among family members, the quality of life of whom can become highly impaired [18[•]]. Cognitive or central sensitization is an additional pathway responsible for generating this vicious cycle, as suggested with food allergies [19^{••}]. In this type of sensitization, misinterpretation of skin sensations, notably itching, occurs in patients with a sensitive nature, causing subsequent extensive activation of cognitive networks in the brain. This further generates stress and anxiety, and hence forms a vicious cycle.

Anxiety and immune status in atopic dermatitis

Elevated IgE levels are found in about 80% of patients with atopic dermatitis. Upon psychological stress, Th2-polarized immunity is enhanced in sufferers of atopic dermatitis, as exemplified by increased production of IgE [20,21]. Atopic dermatitis patients with high IgE levels show significantly higher levels of excitability and inadequate skills to cope with stress compared with those with normal IgE levels [22]; thus, anxiety is handled less well by these individuals. Determining how anxiety tilts immunity to the Th2 type is therefore of importance.

Anxiety can be classified as either state anxiety (anxiety felt at present) or trait anxiety (anxiety felt in general). Anxiety scales are scored from a minimum of 20 to a maximum of 80. We have shown that both trait anxiety and state anxiety are significantly higher in adult atopic dermatitis patients than nonsufferers, with trait anxiety

showing significantly higher scores than state anxiety in the patient group [23^{••}]. Therefore, compared with normal nonatopic individuals, atopic dermatitis patients seem to perceive trait anxiety more intensely than state anxiety. Serum IgE levels are also known to be elevated more in patients with high trait anxiety levels than in those with high state anxiety levels. In accordance with these findings, patients who experience trait anxiety more intensely than state anxiety develop highly Th2-tilted immune responses under stressful conditions. However, anxiety levels are not correlated with the severity of atopic dermatitis as estimated by the SCORAD index, demonstrating the participation of a variety of immune and nonimmune factors in the pathogenesis of atopic dermatitis.

Evidence shows that sufferers of atopic dermatitis are unable to exert a sufficient HPA axis in response to stressful stimulation [11]. Furthermore, responsiveness of β -adrenergic receptors is attenuated in atopic dermatitis patients, as exemplified by disturbances in the cAMP system due to increased cAMP phosphodiesterase activity [24]. As a result of aberrant hormonal responses, cellular immunity is therefore inhibited while immunoglobulin production is augmented in atopic dermatitis patients. Consequently, it is likely that the acute stresses repeatedly affecting atopic dermatitis patients chronically raise anxiety levels, preferentially trait anxiety, stimulating Th2-type responses with enhanced IgE synthesis due to dysregulation of the HPA axis and autonomic nervous system.

Everyday stressors can also cause local immune dysregulation. In the skin, atopy-relevant effector cells such as mast cells and Langerhans cells form a close anatomic relationship with autonomic nerve fibers containing neuroactive substances [25,26]. It is therefore possible that stress-induced secretion of these molecules via direct innervation stimulates these effector cells, thereby modulating atopic dermatitis symptomatology. For example, due to increased phosphodiesterase activity, cAMP levels in leukocytes remain low after binding of catecholamines to their receptors. This results in the release of mediators such as histamine, prostaglandin and leukotrienes, triggering itching and inflammation in atopic individuals.

In asthma, locally released inflammatory mediators have been shown to relay information to the central nervous system through ascending sensory pathways, in addition to influencing the peripheral immune system [27]. It is possible that similar mechanisms operate in skin lesions of atopic dermatitis, where the central nervous system is aberrantly stimulated to lose the ability to control the neuroendocrinological network. Thus, stressful daily events can repeatedly evoke systemic and local

Th2-predominant responses and distort the regulatory immune mechanism, resulting in protracted atopic allergy.

Stress and skin barrier function

Skin barrier function is attributed to the outermost layer of the epidermis, the stratum corneum. The stratum corneum comprises overlapping corneocytes and an intercellular lipid mixture of ceramides, fatty acids and cholesterol [28[•]]. The intracellular space in between corneocytes is filled with keratin filaments intermingled with natural moisturizing factors. In normal skin, the formation of stratum corneum is critically dependent on a steady state between proliferation and differentiation of keratinocytes and desquamation of corneocytes. In contrast, loss of the integrity of intercellular lipids and the disordered production of natural moisturizing factors within the stratum corneum causes dry and scaly skin with abnormal barrier function. Thus, some key stratum corneum functions seem to be co-regulated in response to single common stressors. For example, psychological stress exerts a negative impact not only on permeability-barrier homeostasis but also on stratum corneum integrity and cohesion [29]. Barrier disruption as a result of stress might be ascribed in part to an increase in endogenous corticosteroids and glucocorticoids [30].

In atopic dermatitis, impaired barrier function is related to a global decrease in total ceramides and very-long-chain fatty acid lipids in the stratum corneum [6]. Stress might contribute to the development and amplification of atopic symptoms by further perturbing stratum corneum functions in a stress-axis-dependent fashion. Furthermore, exposure of barrier-disrupted skin to allergens might worsen existing skin lesions in atopic dermatitis patients and provoke eczematous changes in individuals predisposed to atopy.

Control of anxiety and itch management

Pruritus is intense and easily triggered in response to frustration, embarrassment, or other stressful events in atopic dermatitis patients. Moreover, sleep disturbances are commonly attributed to atopic dermatitis, and have been shown to cause both physical and psychological stresses not only in children with atopic dermatitis but also cosleeping parents [31^{••}]. Disturbed sleep has been shown to adversely influence health through psychological and immunological mechanisms [32[•]].

The itch threshold is lowered in atopic dermatitis patients after confrontation with personally relevant negative life events. Moreover, mechanical irritation of the skin, such as scratching, can induce the release of proinflammatory cytokines from keratinocytes, further precipitating itching. Thus, the itch-scratch cycle evolves easily.

Histamines, neuropeptides, proteinases and cytokines generated during cutaneous inflammation are thought to induce itching in atopic dermatitis patients [33]. While both sedating and nonsedating antihistamines offer an advantage, patients do not always benefit from antagonizing histamines, and consequently sedation is often more important than peripheral H1 receptor blockade. Among the various pruritogenic molecules, opioid causes histamine-independent, peripheral itching. It is hypothesized that due to downregulation of opioid receptors in the epidermis, itching is elicited through binding of keratinocyte-derived opioid ligands to their receptors on epidermal unmyelinated nerve fibers [34]. Therefore, itching in atopic dermatitis seems to be either dependent or independent of histamines, involving both peripheral and central components.

Successful control of emotional stresses seems to attenuate itching. Tando spirone is a 5-hydroxytryptamine 1A receptor agonist that exerts anxiolytic and antidepressant effects [35^{*}]. The anxiolytic effect of 5-hydroxytryptamine 1A partial agonists seems to result predominantly from interaction with presynaptic 5-hydroxytryptamine 1A receptors, resulting in a decrease in hyperactive serotonergic neurotransmission [36]. We have shown that in patients who experience trait anxiety, more so than state anxiety, the ratio of trait anxiety score to state anxiety score significantly decreases when tandospirone is added to ongoing treatment [35^{*}]. Moreover, levels of itching were shown to decrease more significantly in the tandospirone-treated group than the nontandospirone group among patients with intense trait anxiety. These data suggest the administration of drugs with an anxiolytic effect as part of the management strategy for stress-associated itching in atopic dermatitis patients.

Conclusion

For many patients, atopic dermatitis is mild and time-limited, and standard therapy including systemic and topical medication is enough to successfully control skin conditions and thus psychological status. However, those with severe and intractable atopic dermatitis, with remissions and exacerbations, often suffer from emotional difficulty and impaired quality of life. The importance of employing a psychological approach to explore the effects of stress on health outcome in allergic and atopic dermatitis patients has thus been increasing. Anxiety is one psychological characteristic of patients with debilitating atopic dermatitis. Many atopic patients have difficulty managing anxiety, of which they are often consciously unaware. Such psychological conditions generate a vicious cycle between anxiety and atopic dermatitis symptomatology. In atopic individuals, the intensity and duration of anxiety levels should therefore be monitored in the context of immune functions and skin

conditions, with the aim of successful stress management. Our challenge for the future is therefore to develop an effective and safe intervention for the treatment of atopic dermatitis. Whereas much can be done to control the disease, psychological interventions are a fundamental component of specialized therapy for all patients with emotional problems.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 396).

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