The interplay between stress and allergy

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Abstract

The nervous and immune systems are interrelated and interacting. Allergy is characterized by a cataract of molecular, cellular and immunological responses activated through specific IgE production to variety of allergens, thus producing symptoms. Stress is a generalized body response to threatening external or internal demands, mobilizing physiological and psychological resources in order to deal with them. Stress activates neuroendocrine and sympathetic system through catecholamine and cortisol secretion, hence influencing the immune system via alteration of Th1/Th2 balance and switching the immune response towards Th2 direction, as in allergic disease. Stressors are capable of modifying the allergic response. In genetically predisposed individuals, stress may both induce the onset of allergic disease and participate in the exacerbation of preexisting allergy. Furthermore, allergic symptoms may lead to a new balance of the cytokine immunoregulation. In conclusion, it seems that a reciprocal influence and relationship between allergic diseases and psychoneuroimmunoendocrine axis exists.

Keywords: *allergy, stress, stress and allergy*, *cytokine, immune system, immune response*

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Introduction

Research data indicate that the nervous and the immune system are reciprocally regulated; a bi-directional communication via neurotrophins is observed. Allergic inflammation is subjected to neuroimmunological regulation, as neurogenic responses may contribute to its pathogenesis [1]. Lately, the research is directed to the enlightenment of the immunoregulatory mechanisms mediating the tolerance towards allergens [2].

During the last decades, a considerable number of studies are accumulated showing the existence of a correlation between nervous and immune system, as well as their mutually regulating relationship [3, 4]. The 'cytokine network of allergy' consists of cytokines acting as messengers of the immune system with various cells of the body, resulting – through a complex interplay – in the development, elicitation and resolution of the inflammation [5]. The secretion of catecholamines and corticosteroids due to the activation of the neuroendocrine and sympathetic systems induced via chronic stress produces Th1/Th2 imbalance enhancing the Th2 mediated response, ultimately switching cytokine expression towards the allergic inflammatory response [3]. Psychological stress may be considered as a social pollutant capable of disrupting physiological pathways interrelated with inflammation by means of mechanisms potentially overlapping with those involving air pollutants and other physical toxicants leading to increased risk for atopic diseases [6].

According to neuroimmunophysiological evidence, stress not only negatively influences immune system protective function but also alters its regulatory function as well [7].

Definitions and pathophysiology of allergic mechanisms

Allergic disease consists of a variety of clinical manifestations with a worldwide increasing impact. Allergy is characterized by the production of specific IgE bound to the mast cells that activates a cascade of molecular, cellular and immunological responses manifested with symptoms from the respiratory tract (rhinitis, asthma), the skin (urticaria, atopic dermatitis), and multiple systems (systemic anaphylaxis) towards a variety of allergens, such as pollens, mites, animal dander, insect venom, food, drugs. It constitutes a chronic non-communicable environmental disease of early onset. Indoor and outdoor risk factors correlated with contemporary life-style and civilization have been described [8].

The universally increasing burden of allergic diseases is considered nowadays as 'the allergy epidemic'. The impact, the consequences and the cost of allergic diseases encountered by all societies are rapidly increasing; detection, prevention and reversal strategies of this phenomenon are required [9, 10].

The term allergy describes a constellation of clinical entities resulting from the immune response to specific antigens – mostly proteins – called allergens. Allergy affects approximately 30% of the world's population. It is characterized by the allergen specific IgE production bounding to the mast cells thus activating a cascade of molecular and cellular events inducing symptoms from different systems as a response to multiple allergens. The underlying pathophysiology involves immunoregulatory dysfunctions similar to those observed in highly stressed populations [11].

In allergy, an overreaction to innocuous allergens exists: through cytokine IL-4 and IL-13 induction, mounting Th2 responses and B-cell class switching to IgE are observed. Furthermore, inadequate immunomodulatory mechanisms contribute to the amplification of the allergic responses [12].

Atopic diseases are complex, polygenic traits thought to be influenced by multiple disease genes, as recent research data have evidenced [13]. Both genetic mechanisms and immunological dysregulation participate in the pathogenesis [14]. Changes in the expression of genetic material can occur through epigenetic modifications induced via DNA methylation, histone modification or microRNA mediated alterations. Studies of asthmatic identical twins showed them to have different epigenetic marks on key immunological genes in their genome [15].

Our understanding of the innate immunity activation during allergen exposure has been enriched through recent ad-

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vances concerning the highly specialized membrane-bound or cytoplasmic pattern recognition receptors (PRRs) – responsible for distinguishing between self and nonself – and their involvement in allergic diseases [16]. Non-antigen specific innate immunity plays important role in adaptation attainment. Innate immune responses initially recognize and respond to external insults through activation of the complement cascade as well as the pro-inflammatory cytokines and chemokines production, thus inducing chronic inflammation [17].

Definitions and pathophysiology of stress mechanisms

Stress can be defined as a generalized body response towards threatening external or internal demands, which mobilizes both physiological and psychological resources in order to deal with them; an imbalance between body demands and coping body capacity characterizes it [3].

According to Selye, stress is the non-specific result of any body or psychic demand is imposed to the laboratory animal [18]. Kaplan characterizes stress as a situation where a great divergence exists among the demands imposed to the organism (losses or threatened losses) and its capacity to respond to them [19].

Stress occurs when homeostasis is threatened or perceived to be so. The stress system, partly located in the central nervous system and partly in peripheral organs, mediates the stress response. Hypothalamic corticotropin-releasing hormone (CRH) and brainstem-derived norepinephrine are interconnected, functioning as the main central effectors of the stress system. Behavioral and somatic disorders are associated with the stress system malfunction. In humans, psychological and pathological conditions are attributed to stress [20].

Stressors are called the events posing the potentially threatening adverse situation that the organism needs to assess and cope with. Such situations can be experienced both in daily life and as major life events. They are considered acute (minutes to hours), sub-acute (less than one

month duration) or chronic (months to years) based on their duration [11].

Impact of stress on the onset and recurrence of allergic symptoms

A common observation among clinicians is the adverse causative relationship between stress and disease in humans. It is generally estimated that approximately 75% of all visits to physicians' offices are related to stress. More specifically, this applies to immune-based dysfunctions, such as allergic diseases [21, 22, and 23]. Research data indicate the stress-induced alteration, both in immune-mediated diseases and in the immune function of the organism in general. A cholinergic activity compared to an adrenergic one seems to predominate in the atopic subjects' autonomic nervous system. Chronic stress promotes the elevation of glucocorticoid levels resulting in an increased cholinergic system function in animals. Corticosteroids affect T helper cells function and inhibit the action of IL-1, IL-2 and IFN-γ, through mechanisms involving the hypothalamus-pituitary axis, enhancing atopy. Moreover, nervous stimulation promotes mast cell degranulation. In addition, stress has been shown to induce specific IgE production in the lungs of sensitized rats, implying a correlation between allergic reaction and stress [24].

Perceived stress and the risk of atopic disorders manifestation have been associated in a dose-depended manner. High stress is in particular correlated with increased risk of asthma incidence, daily asthma medication intake, first-time asthma hospitalization, allergic rhinitis and atopic dermatitis incidence [25].

The hypothalamo-pituitary-adrenal axis plays an important role in the regulation of plasma cytokines and IgE, thus controlling pollen allergy symptoms [26].

Experimental results reveal the role of cortocotropin-releasing factor receptor subtype 1 (CRF_1) in positively signaling stimuli-induced mast cell degranulation and associated in vivo pathophysiologic responses to immunologic and psychologic stress [27].

Prenatal exposure to stress during pregnancy has been correlated with high risk of allergic symptoms in the offspring [11]. The stress-triggered corticosteroids during pregnancy may increase the offspring's susceptibility to allergy [28]. Maternal psychological stress during pregnancy increased the risk of infant wheezing during the first year of life [29].

The negative impact of psychological stress on immunopathology of asthma is currently broadly accepted. Initially, it was estimated that the mechanism of increased cholinergic reactivity coexisting with the increased sympathetic activity of various stress inducing factors was responsible. It seems though that stress may furthermore influence the pathogenesis of allergic diseases and asthma, as an association of higher rates of allergic disorders and depressive symptoms has been observed. It is possible that depression predisposes individuals to allergic symptoms via endocrine and immune dysregulation. It is important to note that depression and stress reduce cellular immunity favoring Th2 immune response and IgE production. Catecholamines also affect allergic diseases and asthma. Norepinephrine is released from postganglionic sympathetic nerve fibers that have a close anatomic relationship with mast cells; it inhibits IL2, IFN-γ and IL-12 production, whilst stimulates IL-6 and IL-10 production. Moreover, the percentage of blood eosinophils of asthmatic students was significantly higher both before and after allergen challenge during examinations compared with the midsemester period. In addition, increased eosinophil counts were measured in the sputum of asthmatic students in response of allergen challenge during high stress period compared to low stress period [21, 22].

An epidemiological longitudinal study on a working-age population sample (17.000 participants, 20-54 years old) representative of the Finnish population was conducted between the years 1998 to 2003 in order to assess the relationship between exposure to stressful life events and the onset of asthma in participants without prevalent asthma or asthma history. A high exposure to severe stressful life events was associated with a 2-fold increased risk of the subsequent onset of asthma as measured by national health registers [30].

A postal survey was conducted in winter 1995-96 among 10667 Finnish first-year university students (18-25 years old). The experience of stressful life events during precedent life periods (previous year, 1-5 years, 6-10 years and over 10 years before) significantly increased the risk of manifestation of asthma, atopic dermatitis and allergic rhinoconjunctivitis in cases compared to controls [24].

Allergy and asthma are characterized by the concomitant deregulation of pro-inflammatory versus anti-inflammatory cytokines and Th1 versus Th2 cytokine balance. This development is influenced both by the patient's genetic and epigenetic susceptibility and the experienced stressors duration and timing. Factors such as stress, viral infections, environmental pollutants and allergy may influence stress response leading to the immune response dysregulation contributing to asthma manifestation. Genes involved in stress and inflammatory response can play a role in the occurrence of asthmatic symptoms. It seems that pro- and anti- inflammatory cytokines contributing to the pathopsysiology of the allergic disease – despite the target organ – are conversely correlated to cortisol production [20, 31].

Approximately 30% of the patients consider the psychological factors capable of triggering their asthmatic symptoms [32].

Stress-induced asthma exacerbations may be related to alterations in the function of the autonomous nervous system and immune response in adults and also in children. Alpha-sympathetic and parasympathetic activity cause bronchoconstriction. After the stress abates a parasympathetic rebound often follows the stress-induced sympathetic activation. In addition, stress and depression – often observed as co-morbidity in asthmatic patients – influence the severity of asthmatic symptoms also indirectly, through the disorganization of self-care behavior of the individual [33].

Research evidence suggests that a causal association between chronic psychosocial stress and asthma manifestation or asthma morbidity exists. Changes in the methylation and expression of genes regulating behavioral, autonomic, neuroendocrine, and immunologic responses to stress have

been implicated as underlying mechanisms. Furthermore, it seems that susceptibility genes predispose young people experiencing chronically stress to post-traumatic stress disorder, as well as asthma. The correlation between stress and asthma is complicated. Stress may indirectly affect asthma through exposure to cigarette smoking, outdoor air pollution, compliance to treatment, family support and coping mechanisms. However, the most influential impact of stress on asthma relies in its direct action on pathogenic mechanisms in the airways. It modulates lung development, neuroendocrine and autonomic nervous system responses, and the immune system. Research data indicate that stressors – when perceived as threatening and unmanageable – modify HPA (hypothalamic-pituitary-adrenocortical) axis and ANS (autonomic nervous system) activity. This action is mediated through CRH (corticotrophin-releasing hormone) secretion from the paraventricular nucleus of the hypothalamus that enhances the adrenocorticotropic hormone which signals the adrenal glands to synthesize and release cortisol. Stress – via the alteration of the outflow of the sympathetic and parasympathetic system – changes the systemic balance and concentration of glycocorticoids and catecholamines; it also alters gene expression through the ligation of the functional receptors of macrophages and lymphocytes to those hormones. Therefore, stressors potentiate reactivity to asthma triggers, such as allergens and infections, eventually exacerbating airway inflammation and airflow obstruction. Recent research focuses on the role of allelic variation in genes regulating stress responses [34].

Stress is considered a significant factor in asthma exacerbation, since brain responses to stress have immunomodulatory action on allergic asthma. More specifically, Th2-type lung inflammation, known to be induced by stress, is strongly correlated with asthma pathogenesis. Stress enhances eosinophilic airway inflammation through activation of the HPA axis and the autonomic nervous system, leading to the secretion of stress hormones (glucocorticoids, epinephrine and norepinephrine) into the blood, resulting in the predominance of Th2 and Th17 response [35, 36, 37].

A subgroup of asthma patients who may be less respon-

sive to steroid treatment has been recently recognized: a TH17-mediated neutrophil-predominant phenotype. Additional mechanisms of steroid resistance have been described. Increased activity of glucocorticoid receptor (GR) phosphorylating kinases modify the interactions of GR with transcription factors in order to inhibit the ability of GR to bind with the glucocorticoid response element (GRE), thus increasing pro-inflammatory gene transcription. Moreover, oxidative stress modifies transcription factors and cofactors (P13K, for example) leading to the inhibition of histone deacetylase 2, favoring, as a result, the increase of pro-inflammatory compared to anti-inflammatory gene transcription [37].

In laboratory studies, about 20% of asthmatic patients showed airway constriction after exposure to emotional stress, attributed to parasympathetic involvement. The interaction between nerves and mast cells is considered to contribute both to the immediate and late asthmatic response. Moreover, the stress-induced increased IgE production and susceptibility to infections seem to also influence the manifestation of asthmatic symptoms [38].

Stressful life events (divorce, for example) and interpersonal conflicts can increase asthma risk, possibly via an immunological pathway [39].

Modern highly stressful lifestyle conditions may increase the occurrence of allergic rhinitis symptoms [6, 40].

Clinical cases, where patients develop acute urticaria after experiencing a stressful condition, such as an earthquake, have been reported. Psychological factors have been suggested to play a role both in the onset and the exacerbations of urticaria, possibly due to the increased plasma concentrations of norepinephrine, epinephrine, prolactin and dopamine [41]. Persistent perceived emotional stress has been correlated with allergy flares manifestation [42]. Chronic stress can contribute to chronic urticaria symptoms via systemic inflammation and lower basal costisol levels compared to controls [43, 44]. Recent studies report that stress contributes to the onset and continuing of urticaria symptoms. Psychoneuroimmunologic research indicates that the 'mind-brain complex' influences the immune system [45].

Several studies show that stress aggravates acute and chronic atopic dermatitis symptoms and co-morbidity with psychopathology is often reported. Hormonal factors, such as attenuated growth hormone secretion and blunted cortisol response in atopic individuals compared to controls, have been implicated in the explanation of this correlation. The hyporesponsiveness observed in the HPA axis may be partially responsible for the stress-induced exacerbations of atopic dermatitis. Moreover, skin arterioles' dilatation because of stress can increase pruritus during the periods that the patient experiences stress [41]. Immunoregulatory mechanisms seem to be less effective in people experiencing stressful events, leading to atopic dermatitis exacerbations, possibly through hypo-reactivity of the HPA axis [46]. A systemic atopic inflammation is probably involved [47]. Pruritus, a main characteristic symptom of atopic dermatitis and allergy in general, is mediated via release of multiple factors, such as histamine, neuropeptides – SP, VIP, NPY, NK1R – acetylcholine, tryptase, IL-31, GRPR, and others, influencing the peripheral nerve endings, the dorsal root ganglia, the spinal cord and the CNS [48].

Impact of allergy on stress and effects on the psychological 'well-being' of the allergic patients

Allergic diseases significantly impair quality of life. Recent studies show that allergy may induce stress, anxiety and depression. Even though allergic diseases are rarely fatal, they have considerable psychological impact on patients' everyday life [49].

Patients suffering from asthmatic symptoms have more psychological problems – stress and anxiety – and a lower quality of life compared to the general population [50]. Asthma has negative consequences to the patients' somatic and psychic health, as well as their social relationships [51]. Furthermore, asthma decreases life satisfaction of the individual [52].

Allergic rhinitis has been associated with significant impairment of the patients' psychological well-being; they score higher than controls as far as it concerns feelings of insufficiency, somatization complaints, sleep disturbances, and depression [53].

Approximately 19% of the patients suffering from allergic rhinitis symptoms that have visited the allergy clinic complained of anxiety and/or depression as well [54].

Moreover, allergic rhinitis has a significant impact on the quality of life of both adolescents and adults, thus intensifying the vicious cycle [55, 56].

Patients suffering from chronic urticaria experienced significantly higher stress levels in comparison to the control group [57].

Atopic dermatitis is a burden for the patients and it deteriorates intensively their quality of life [47].

The vicious cycle of the bi-directional interaction of stress and allergy

The relationship between psychological factors and allergy has been an issue of interest for several decades. The personalities of allergic individuals have been described and psychological treatment of allergic patients has been attempted [58]. Accumulative evidence illustrates lately the psychological and social impacts of allergic disease on patients and their families. On the other hand, stress has been identified as triggering factor for allergic asthma and atopic dermatitis, whereas patients suffering from asthmatic exacerbation develop stress [59].

Research evidence suggests that chronic stress activates the neuroendocrine and the sympathetic systems through catecholamine and cortisol secretion influencing the immune system and modifying the Th1/Th2 balance switching the immune response to Th2 direction, as is the case in the allergic disease. Clinical observations describe that stressors are capable of altering the allergic response. It could be considered that in individuals with atopic predisposition chronic stress may enhance the development of allergic disease and also complicate the control of preexisting allergic symptoms. On the other hand, the manifestation of al-

lergic symptoms leads to further imbalance of the cytokine immunoregulation [60]. Epidemiological studies exploring the possible bilateral association between psychosocial factors and atopic diseases have been conducted lately. A systematic review and meta-analysis of 43 prospective cohort studies examined the effect of psychosocial parameters on atopic disorders and the impact of atopic diseases on mental health. In the majority (90.7%) of cases patients suffering from asthma and rhinitis were evaluated. A positive correlation was observed between psychosocial factors and future atopic disease manifestation (p<0,001) as well as between atopic disorder and future poor mental health (p<0,001). Furthermore, it seems that psychosocial factors exhibit both etiological and prognostic impact on atopic diseases [61].

Co-morbidity

Co-morbidity between psychological dysfunctions – stress, anxiety, and depression – and allergic diseases, such as asthma, urticaria and atopic dermatitis has been described. Review studies indicate that anxiety and depression significantly increased the risk of allergic asthma development [62, 63]. Chronic urticaria patients often suffer from anxiety and depressive disorders as well [64].

The psychological profile of the allergic patient

Atopic patients are characterized by increased emotional sensitivity and a depressive psychological profile [65]. Psychological traits including depression, hypochondriasis, hysteria, anxiety, and social introversion are observed more frequently in allergic patients in comparison to the general population [66].

Focusing on the history of the patient

While interviewing the patient, it is important, except for the history concerning allergic symptoms, to also inquire details about the general life condition and well being. Questions referring to the medical history and the onset of the disease, as well as the family, social and cultural environment contribute to the collection of valuable information. Important issues consist of the living conditions, the habits, substance use, precedent and coexisting diseases, professional, family and social activities, stress, general perceptions and attitude of life. Seeking detailed description of the present and past mental status of the patient clarifies personality traits and ways of life issues management, possibly contributing to the onset and relapse of the patient's allergic symptoms. The observation of the patient's general attitude and response to the interview with the doctor can reveal unrealized psychological difficulties and dysfunctions capable of deteriorating the symptoms [67, 68].

The therapeutic and preventive value of the simultaneous assessment and management of somatic and psychic problems of the allergic patient

According to the World Health Organization, 'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. The multidimensional approach, evaluation and management of the allergic patient and his/her family within biological, psychological and social context, significantly contribute both to the therapeutic symptom control and the prevention of the allergic disease.

In conclusion

An interaction between allergic diseases and psychoneuroimmunoendocrine axis seems to exist. The bidirectional relationship of allergic symptoms on the one hand and psychosocial factors on the other, indicates that, besides environmental control, medicines and immunotherapy, psychotherapeutic interventions might also contribute to the management and prevention of the allergic disease.

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